

Total Synthesis of the 7-3'-Linked Naphthylisoquinoline Alkaloid Ancistrocladidine

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Abstract

This thesis describes the first total synthesis of ancistrocladidine, a member of the naphthylisoquinoline class of natural products. In Chapter 1 the synthetic challenges presented by the naphthylisoquinoline alkaloids are discussed and strategies that have been adopted in previous syntheses of naphthylisoquinoline alkaloids are overviewed.

Chapter 2 identifies 6-alkoxybenzocyclobutenones as useful precursors to the naphthalene core of the naphthylisoquinoline alkaloids. An efficient preparation of 6-alkoxybenzocyclobutenones is developed. Following this, these compounds are utilised in the synthesis of naphthalene building blocks, which are key intermediates in the total synthesis of naphthylisoquinoline alkaloids.

Chapter 3 describes the synthesis of functionalised dihydroisoquinoline precursors. Following this, an investigation into the formation of the 7-3' bond is carried out by reaction of the aforementioned intermediates with 6-methoxybenzocyclobutenone, whose synthesis is described in Chapter 2. Unfortunately, the key bond could not be formed using this approach.

Following this, Chapter 4 describes an alternative approach to biaryl bond formation that utilises a lead-mediated biaryl coupling. This was used to successfully form the key 7-3'-biaryl bond of ancistrocladidine and the remainder of this chapter describes the completion of an enantioselective total synthesis of the natural product.

Chapter 5 summarises the above results and discusses the future potential of this research.

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Abbreviations

abs	Absolute
Ac	Acetyl
acac	Acetylacetonate
AD	Asymmetric Dihydroxylation
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
BHA	3- <i>t</i> -Butyl-4-hydroxyanisole
Bn	Benzyl
Bp	Boiling point
br	Broad
Bu	Butyl
BTMA	Benzyltrimethylammonium
Calcd	Calculated
cat	Catalytic
Conc	Concentrated
δ	Chemical shift in parts per million downfield from tetramethylsilane
d	Doublet (NMR)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[4.3.0]non-5-ene
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethylformamide
DMG	Directed metalation group
ee	Enantiomeric excess
Et	Ethyl
g	Gram(s)
h	Hour(s)

HIV	Human immunodeficiency virus
HMPA	Hexamethylphosphoric triamide
HPLC	High-pressure liquid chromatography
HRMS	High-resolution mass spectrometry
imd	Imidazole
<i>J</i>	Coupling constant (NMR)
IR	Infrared
LDA	Lithium diisopropylamide
LG	Leaving group
LICA	Lithium cyclohexylisopropylamide
m	Multiplet (NMR)
Me	Methyl
MHz	Megahertz
min	Minutes
MOM	Methoxymethyl
Mp	Melting point
Ms	Methanesulfonyl
MTPA	α -Methoxy- α -trifluoromethylphenylacetic acid
NBS	<i>N</i> -Bromosuccinimide
NOE	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
PPA	Polyphosphoric acid
PPE	Polyphosphate ester
ppm	Parts per million
ppt	Precipitate
Pr	Propyl
q	Quartet (NMR)
r.t.	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
sat	Saturated
S _N	Nucleophilic substitution
S _N Ar	Nucleophilic aromatic substitution
TBAF	Tetrabutylammonium fluoride

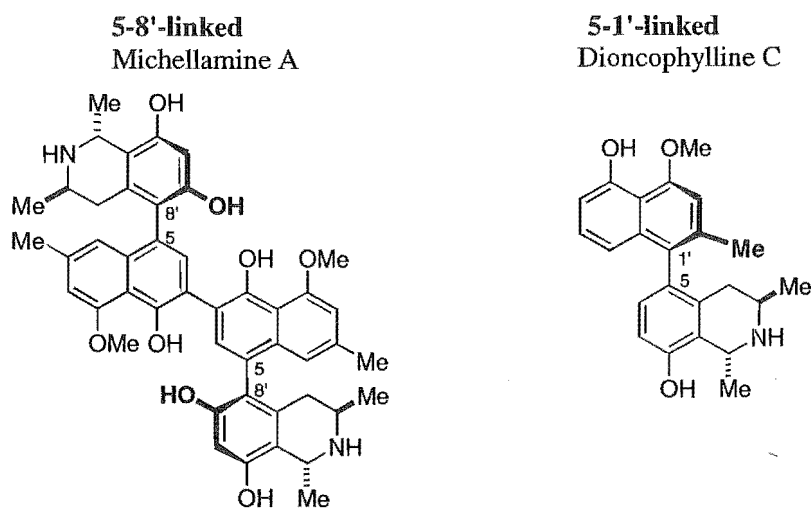
TBS	<i>t</i> -Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
Ts	<i>p</i> -Toluenesulfonyl

Chapter One

Introduction

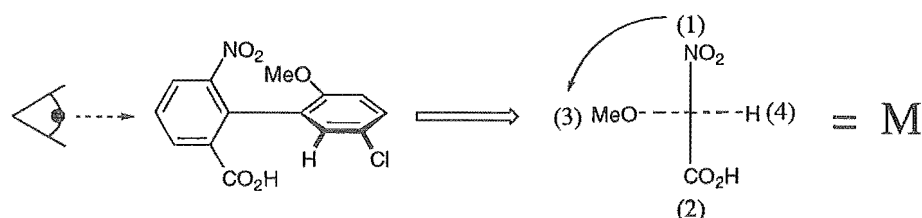
1.1 General Introduction

The naphthylisoquinoline alkaloids are a large group of natural products whose only known source are the *Ancistrocladaceae* and the closely related *Dioncophyllaceae* plant families.¹ These natural products contain, as the name suggests, both a naphthalene and isoquinoline moiety, which are connected by a biaryl bond. Due to the hindered nature of this biaryl bond, restricted rotation dictates that many of these compounds exist as thermally stable atropisomers.^{*,2} These natural products can be grouped according to the position of the biaryl bond linking the naphthalene and isoquinoline structural entities. Shown below are representative examples of each type of linkage, chosen so as to illustrate the structural diversity present within this class of compounds (**Figure 1.1**).



* Molecules with chiral axes may be viewed as helices and their configuration denoted as *M* or *P*. For this designation the ligands of highest priority (Cahn-Ingold-Prelog) in front (1 and 2) and in the back (3 and 4) of the framework are considered. If the turn from priority front ligand 1 to priority rear ligand 3 is clockwise, the configuration is *P*, if anticlockwise it is *M*.

e.g.



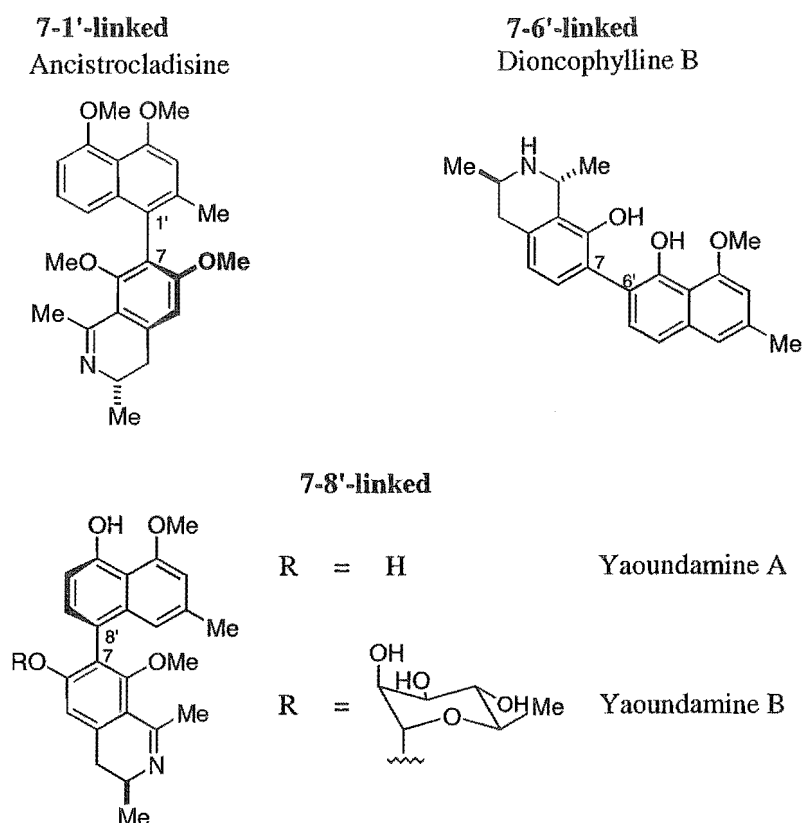


Figure 1.1 Representative naphthylisoquinoline alkaloids.

Central to the discovery and interest in these compounds is their pronounced and diverse biological activity. Several of the plant families containing these alkaloids have been used as traditional medicines for the treatment of dysentery and malaria.³ More recently, bioassay-directed isolation has led to the discovery of many structurally related compounds whose biological activities include antimalarial,⁴ antifeedant,⁵ molluscidal,⁶ insect growth-retarding,⁷ and anti-HIV activity.^{5b, 8} The potent anti-HIV activity of the naphthylisoquinoline alkaloid michellamine B lead the National Cancer Institute to select it for preclinical development.^{8e} Accordingly, chemical syntheses of the natural products, coupled with structure-activity guided modifications, has been a fruitful area of investigation for the development of more selective and active drugs.⁹

By synthesising these challenging organic molecules the limitations of established synthetic methodology are revealed. Along with this, situations arise that require new methods of forming and manipulating chemical bonds. Important issues that have emerged in the synthesis of naphthylisoquinoline alkaloids are as below:

- Stereoselective synthesis of the isoquinoline moiety.
- Synthesis of the naphthalene portion.
- Formation of the biaryl bond linking the naphthalene and isoquinoline entities, with a view to stereoselective formation of atropisomers.

What follows is a summary of key strategies, which have been used to address the above issues in total syntheses of naphthylisoquinoline alkaloids.

1.2 Strategies Utilised in the Total Synthesis of Naphthylisoquinoline Alkaloids

1.2.1 Synthesis of the Heterocyclic Moiety

The main functionality present in the heterocyclic portion of the naphthylisoquinoline alkaloids is illustrated below (**Figure 1.2**).



Figure 1.2 Heterocyclic portions of naphthylisoquinoline alkaloids.

Key features include:

- A *meta*-oxygenation pattern at C6 and C8 on the aromatic moiety, although the C6-oxygen functionality may be absent.
- A 3,4-dihydro- or tetrahydroisoquinoline ring.
- A stereocentre at C3, or C1 and C3.

The established method for formation of the dihydroisoquinoline ring is the Bischler-Napieralski cyclisation.¹⁰ Generally, tetrahydroisoquinoline ring systems are derived from the appropriate dihydroisoquinoline moiety, by reduction with metal hydrides, but occasionally the Pictet-Spengler reaction has been utilised to directly assemble the tetrahydroisoquinoline array (**Figure 1.3**).

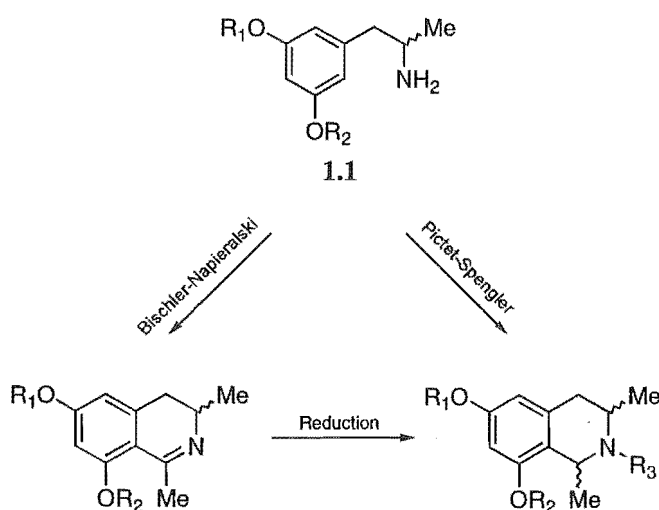
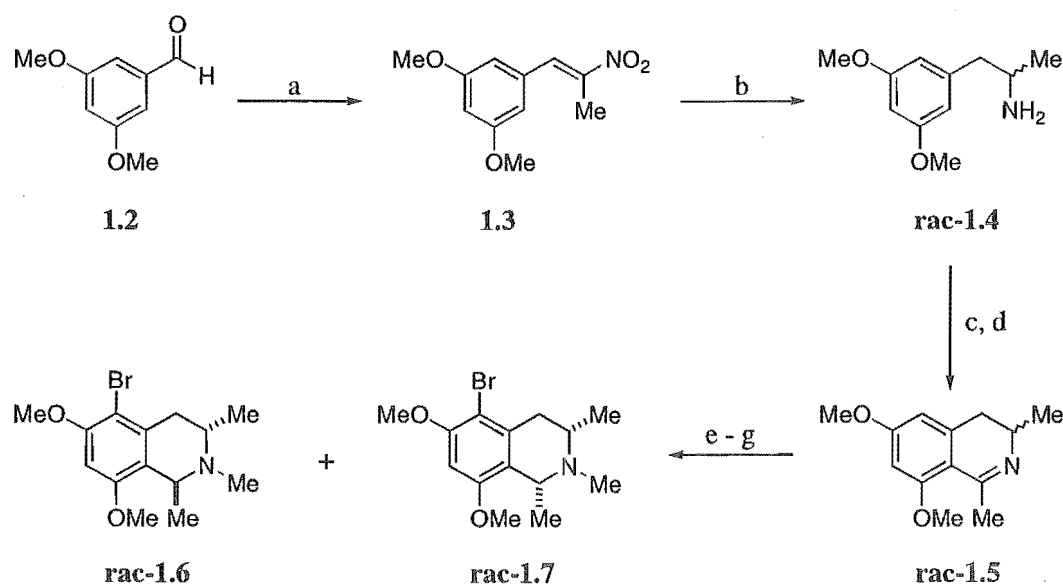


Figure 1.3 Preparation of heterocyclic compounds.

The key intermediate for preparation of these heterocycles is the amphetamine **1.1** shown above. Several procedures have been developed to prepare such an intermediate and are discussed below.

1.2.1.1 Introduction of Nitrogen Functionality *via* the Henry Reaction

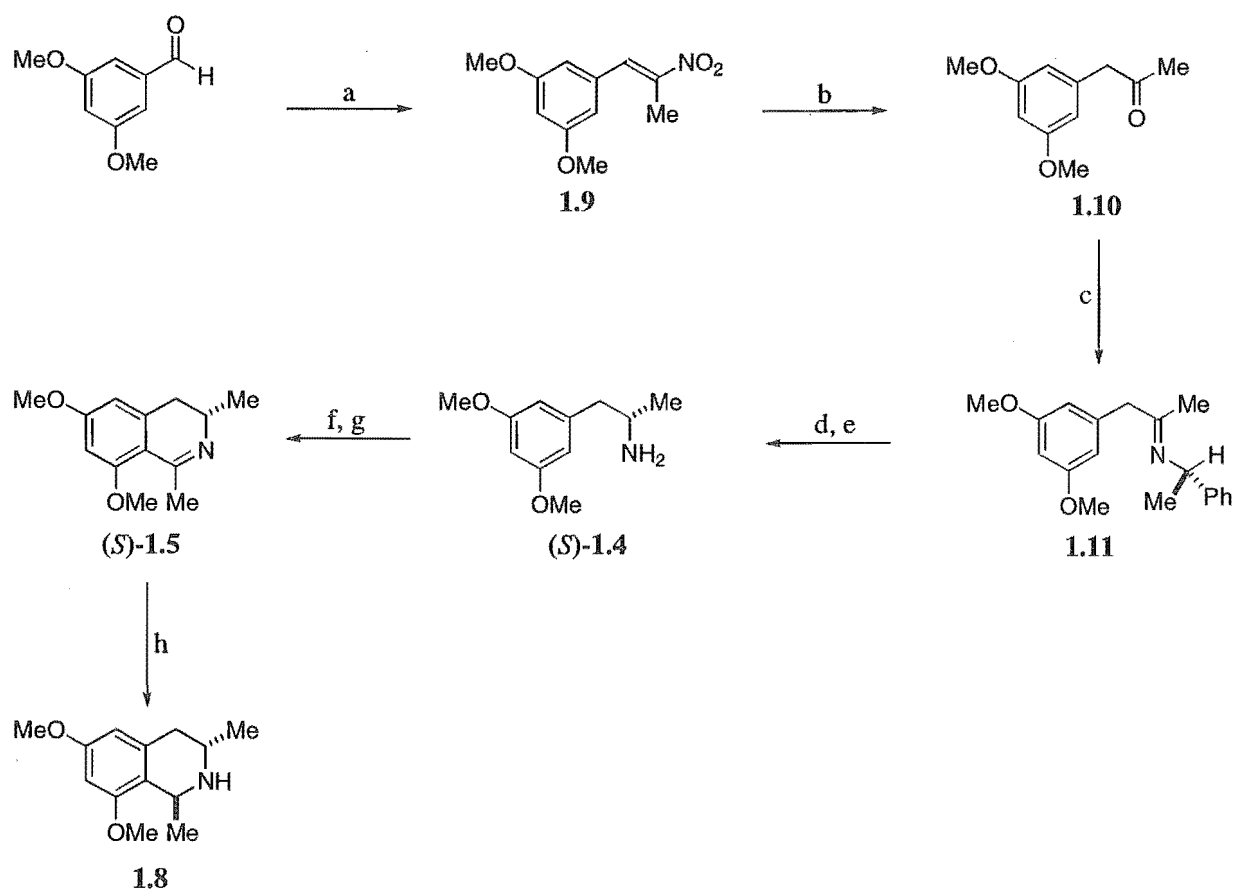
In a projected total synthesis of *Ancistrocladus* naphthylisoquinoline alkaloids, Sargent and Rizzacasa planned to displace a methoxy group of a chiral naphthylloxazoline with an appropriate Grignard reagent. Accordingly, they required access to a functionalised tetrahydroisoquinoline. Their approach began with a Henry reaction on aldehyde **1.2** (Scheme 1.1).¹¹ The resulting nitrostyrene **1.3** was reduced using lithium aluminium hydride yielding the desired amine **rac-1.4**. Subsequent acetylation and Bischler-Napieralski cyclisation gave dihydroisoquinoline **rac-1.5**. Methylation of the imine and reduction resulted in a separable mixture of *cis*- and *trans*-tetrahydroisoquinolines. These isomers were regioselectively brominated to give tetrahydroisoquinolines **1.6** and **1.7**, precursors to the desired Grignard reagents. Although the reactions leading to the dihydroisoquinoline are all high yielding, the lack of stereocontrol, in the reduction of both the nitrostyrene and the dihydroisoquinoline, have limited the utility of this approach.



Scheme 1.1 Reagents and yields: (a) NH_4OAc , HOAc , EtNO_2 , 98 %; (b) LiAlH_4 , THF, 94 %; (c) AcCl , NEt_3 , CH_2Cl_2 , 98 %; (d) POCl_3 , CH_3CN , 96 %; (e) CH_3I , EtOAc , 84 %; (f) NaBH_4 , EtOH , *cis* 29 %, *trans* 59 %; (g) Br_2 , CH_2Cl_2 , 68 % for **rac-1.6**, 65 % for **rac-1.7**.

Bringmann has pioneered a popular route to chiral heterocyclic building blocks such as (*S*)-**1.5** and **1.8** (Scheme 1.2).¹² This, as above, involved introduction of the nitrogen functionality *via* the Henry reaction. Subsequent reduction of nitrostyrene **1.9** with iron powder gave the ketone

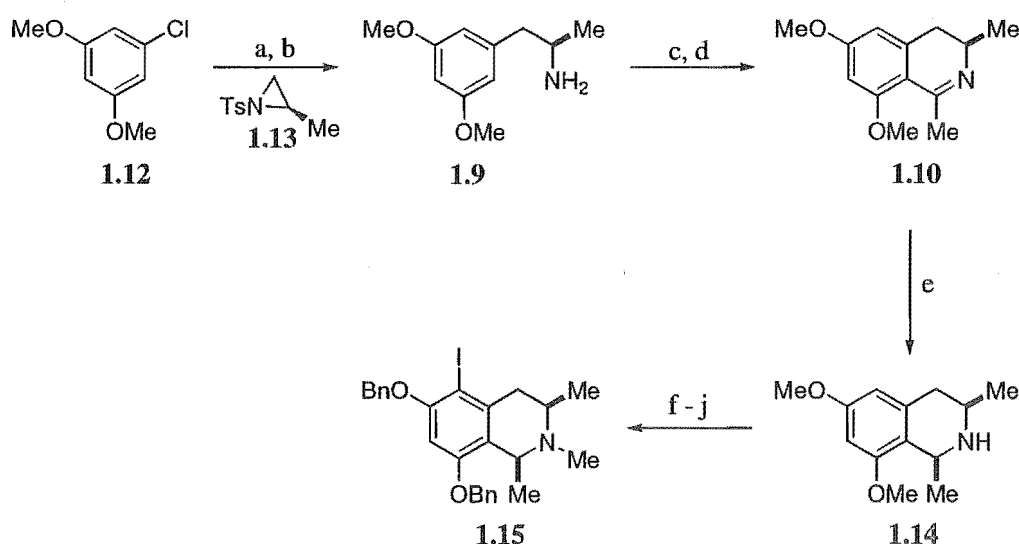
1.10, which upon reaction with (*S*)-methylbenzylamine gave the chiral imine **1.11**. Stereoselective hydrogenation with Raney nickel, followed by deprotection, liberated the chiral amine (*S*)-**1.4**, which was readily converted into the desired dihydroisoquinoline (*S*)-**1.5** by the standard procedure. Stereoselective reduction with $\text{LiAlH}_4/\text{AlMe}_3$ gave access to *trans*-tetrahydroisoquinoline **1.8** in 85 % yield and 92 % diastereomeric excess (de). Although the reaction conditions are not exceedingly tolerant of functionality, and the imines are often reported as unstable brown oils, chromatography can be avoided by carrying intermediates through and by purification of the amines as their hydrochloride or hydrobromide salts.



Scheme 1.2 Reagents and yields: (a) NH_4OAc , HOAc , EtNO_2 ; (b) Fe/HOAc ; (c) (*S*)-1-Phenylethylamine, toluene; (d) Raney Ni, EtOH; (e) H_2 , Pd-C, MeOH, 84 %, 92 % de; (f) AcCl , NEt_3 , CH_2Cl_2 ; (g) POCl_3 , CH_3CN , 76 %; (h) $\text{LiAlH}_4/\text{AlMe}_3$, THF, 85 %, 92 % de.

1.2.1.2 Introduction of Chirality *via* the Reaction of Grignard Reagents with Chiral Electrophiles

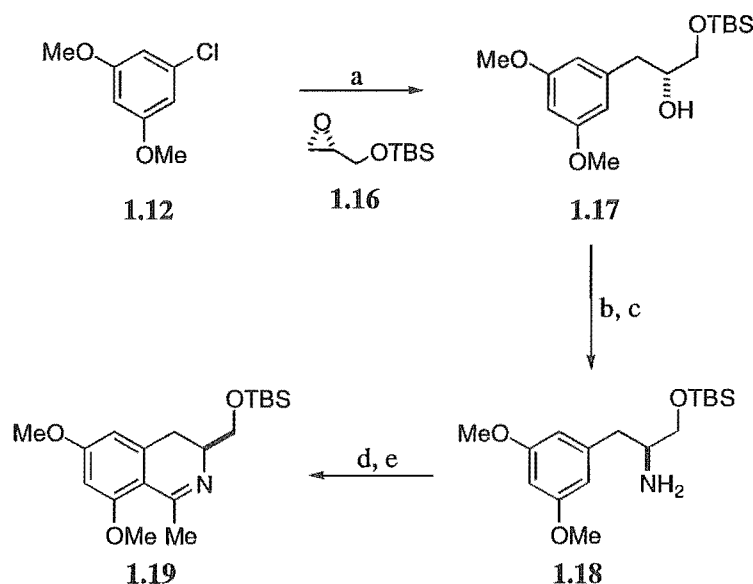
The shortest route to the chiral amphetamine building block is that developed by Hoye and Chen (Scheme 1.3).¹³ The Grignard reagent derived from aryl chloride **1.12** was converted into an aryl cuprate, which upon reaction with aziridine **1.13**, and subsequent deprotection gave the enantiomerically pure primary amine (*R*)-**1.4** in 79 % yield. This is a highly efficient procedure and the availability of either enantiomer of the aziridine allows access to both enantiomers of the amine building block. The amine was readily converted into the dihydroisoquinoline (*R*)-**1.5** by the standard acetylation/cyclisation protocol. Hydrogenation gave the *cis*-configured tetrahydroisoquinoline **1.14**, which was smoothly converted into an appropriately functionalised *N*-methyl derivative **1.15**, for use in a palladium-catalysed biaryl bond formation strategy. Although this is a short efficient route, the compatibility of Grignard-forming conditions with sensitive functional groups may hamper the utility of this approach.



Scheme 1.3 Reagents and yields: (a) Mg, THF, CuBr•SMe₂, **1.13**, 100%; (b) Na/NH₃, 79 %; (c) Ac₂O, NEt₃, 99%; (d) POCl₃, CH₃CN, 82 %; (e) H₂, Pd/C, 93 %; (f) BBr₃, CH₂Cl₂, 99 %; (g) 2.1 eq TESCl, NEt₃, CH₂Cl₂, ClCO₂Et, TBAF, THF, 87 %; (h) BnBr, K₂CO₃, 72 %; (i) LiAlH₄, 94 %; (j) I₂, Ag₂SO₄, EtOH, 80 %.

Lipshutz and Keith synthesised their functionalised heterocyclic portion by allowing the Grignard reagent derived from chloride **1.12** to react with commercially available (*S*)-TBS-glycidol (**1.16**) to give alcohol **1.17**.¹⁴ Nitrogen functionality was introduced by Mitsunobu inversion with phthalimide, followed by deprotection to give chiral amine **1.18**, which was

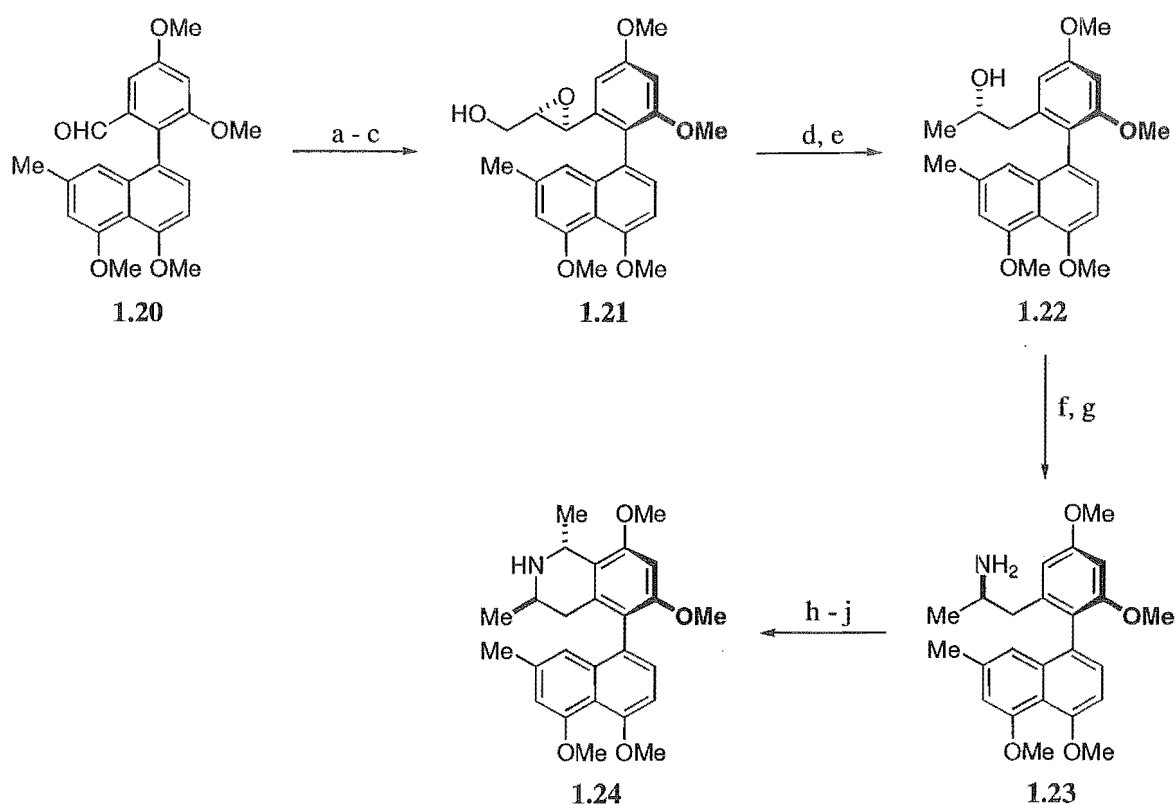
readily converted into dihydroisoquinoline **1.19** using similar chemistry to that described earlier in this section (Scheme 1.4). A useful feature of this sequence is the ability to retain a labile protecting group, such as a TBS (*t*-butyldimethylsilyl) ether, throughout the synthesis. In particular, by addition of 2,4,6-collidine as an acid scavenger, the TBS group withstands the rather harsh conditions of a Bischler-Napieralski cyclisation.



Scheme 1.4 Reagents and yields: (a) Mg, THF, (*S*)-TBS-glycidol (**1.16**), 10 % CuBr•SMe₂, 92 %; (b) phthalimide, PPh₃, DEAD, THF, 88 %; (c) H₂NNH₂, EtOH, 89 %; (d) Ac₂O, NEt₃, CH₂Cl₂, 99 %; (e) POCl₃, CH₃CN, 2,4,6-collidine, 97 %.

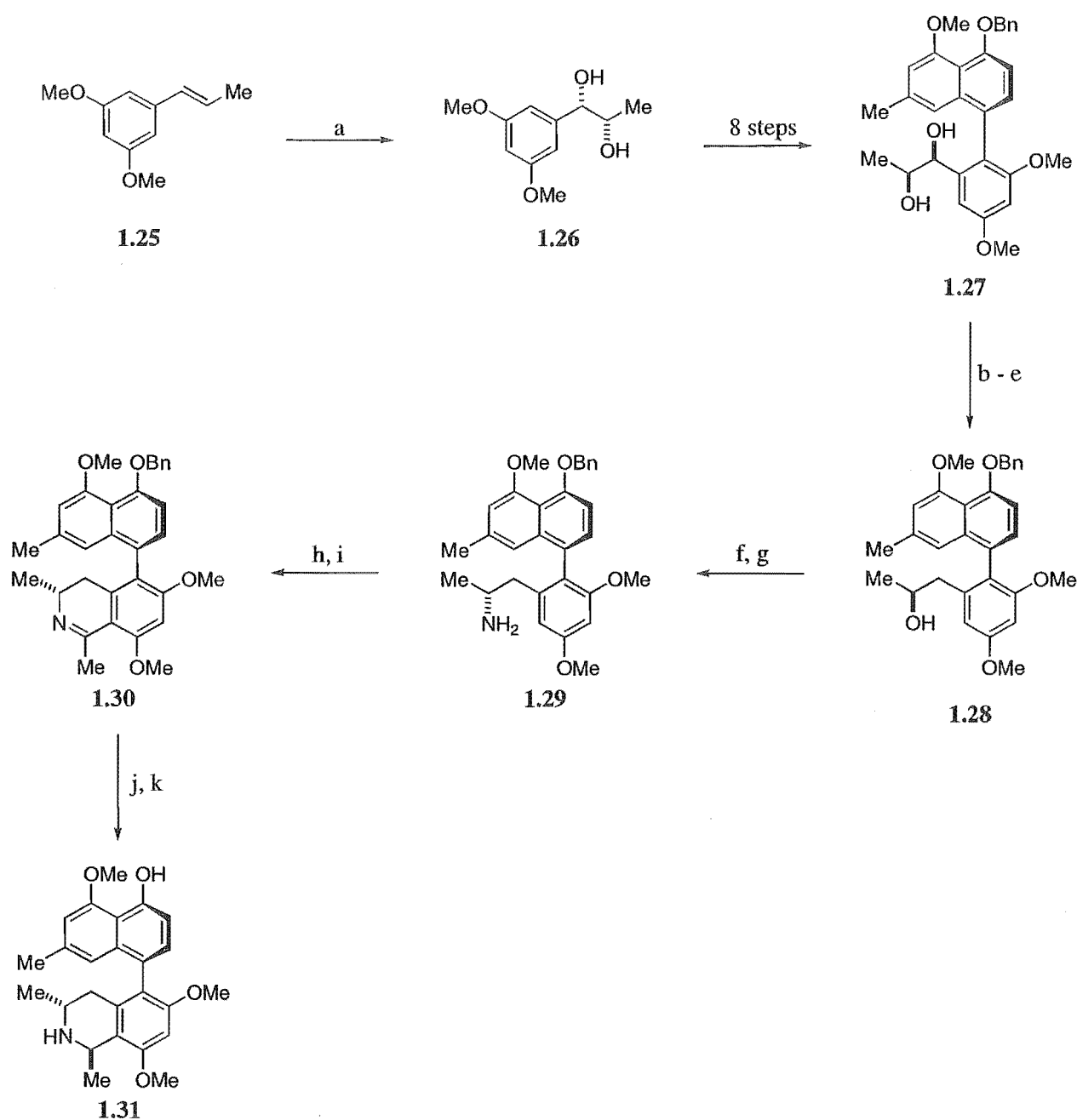
1.2.1.3 Introduction of Chirality *via* Functionalisation of Double Bonds

The Sharpless asymmetric epoxidation has been used to introduce the appropriate stereochemistry by the group of Rao (Scheme 1.5).¹⁵ In their synthesis biaryl aldehyde **1.20** was converted into an allylic alcohol and, using the Sharpless methodology, gave a 1:1 mixture of atropisomeric epoxides **1.21** (only one shown). Mesylation and reduction gave the alcohol **1.22**. Mitsunobu inversion followed by deprotection gave the chiral amine **1.23**, which was readily converted into *O,O,O*-trimethylkorupensamine A **1.24**.



Scheme 1.5 Reagents and yields: (a) $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, NaH, C_6H_6 ; (b) DIBAL, CH_2Cl_2 , 70 % over 2 steps; (c) (+)-DIPT, $\text{Ti}(\text{O}^i\text{Pr})_4$, $t\text{BuOOH}$, CH_2Cl_2 , molecular sieves, 85 %, >95 % ee; (d) MsCl , NEt_3 , CH_2Cl_2 ; (e) LiAlH_4 , THF, 91 % over 2 steps; (f) $(\text{PhO})_2\text{PON}_3$, PPh_3 , DEAD, C_6H_6 , 83 %; (g) Pd-C, H_2 , EtOAc ; (h) Ac_2O , EtOAc , 89 % over 2 steps; (i) POCl_3 , CH_3CN ; (j) $\text{AlMe}_3/\text{LiAlH}_4$, 70 % over 2 steps.

Asymmetric dihydroxylation has also been utilised as a method for introduction of chirality into naphthylisoquinoline alkaloid systems (**Scheme 1.6**).¹⁶ Dihydroxylation of alkene **1.25** gave diol **1.26** in 99 % yield and 98 % enantiomeric excess (ee). Following an eight-step procedure for formation of the biaryl bond, the biaryl diol **1.27** was selectively protected as a silyl ether. The benzylic hydroxyl was removed, followed by a desilylation to give alcohol **1.28**. Mitsunobu inversion and reduction of the azide gave the enantiomerically pure amine **1.29**, which was readily converted into the dihydroisoquinoline **1.30**. Reduction and deprotection gave optically pure *O,O'*-dimethylkorupensamine A **1.31**.



Scheme 1.6 Reagents and yields: (a) AD-mix- α , $\text{CH}_3\text{SO}_2\text{NH}_2$, $t\text{-BuOH}$, H_2O , 99 %, 98 % ee; (b) TBSCl, imidazole, DMF, 84 %; (c) $(\text{imd})_2\text{C}=\text{S}$, THF; (d) $n\text{-Bu}_3\text{SnH}$, AIBN, 62 % over 2 steps; (e) TBAF, THF, 96 %; (f) $(\text{PhO})_2\text{PON}_3$, DEAD, PPh_3 , THF; (g) SnCl_2 , MeOH; (h) Ac_2O , pyridine, 66 % over 3 steps; (i) POCl_3 , CH_3CN ; (j) $\text{LiAlH}_4/\text{AlMe}_3$, THF, 70 % over 2 steps; (k) Pd-black, HCO_2H , MeOH, 91 %.

It is evident that a number of useful methods are available for the preparation of functionalised chiral dihydro- and tetrahydroisoquinoline moieties. The last two methods discussed are particularly useful due to the reliability and predictability of the asymmetric epoxidation and dihydroxylation procedures. The compatibility of these sequences with a range of functionality

is noteworthy. Accordingly, this would make them suitable for application to other naphthylisoquinoline alkaloid syntheses.

1.2.2 Synthesis of the Naphthalene Core

The naphthalene core common to the naphthylisoquinoline alkaloids is represented below in **Figure 1.4**. The key features are oxygenation at positions 1 and 8, and a methyl group in the 3-position. Numerous methods exist for the construction of this core, all of which possess their relative merits. What follows is a discussion of the methods that have been used to construct this molecular entity in relation to the total synthesis of naphthylisoquinoline alkaloids.

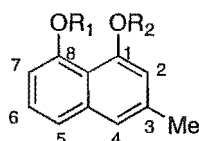


Figure 1.4 The naphthalene core of naphthylisoquinoline alkaloids.

1.2.2.1 Cyclisation *via* Diels Alder Reactions

The most widely used procedure for the synthesis of naphthalene precursors was introduced by the group of Watanabe *et al.*¹⁷ It involves a Diels-Alder reaction between a benzyne, generated *in situ*, and an appropriately functionalised diene. This was developed further by Hoye *et al* to include aryl-dihalides as benzyne precursors (**Figure 1.5**).¹⁸ The naphthalene core **1.32** (P = Me) is generated in one step by reaction of the dienolate **1.33** (generated from the reaction of *N,N*-diethyl-3,3-dimethylacrylamide with *n*-BuLi), with 3-bromo-6-methoxybenzyne (generated from the reaction of lithium cyclohexylisopropylamide (LICA) with 2,4-dibromoanisole (**1.34**). The reaction is low yielding (21-26 %), but remarkably, the sideproducts identified are all derived from 3-bromo-6-methoxybenzyne indicating no formation of the regioisomeric 3-bromo-4-methoxybenzyne. This procedure has been used to prepare MOM-protected naphthol **1.32** (P = CH₂OMe), also. In both cases chromatographic purification on large-scale preparations has proven to be cumbersome.

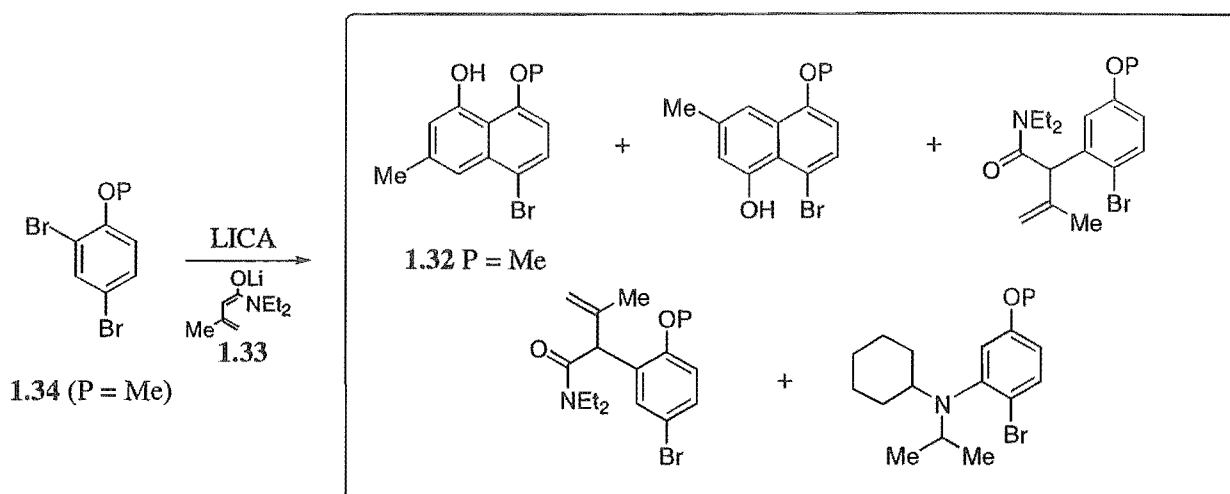
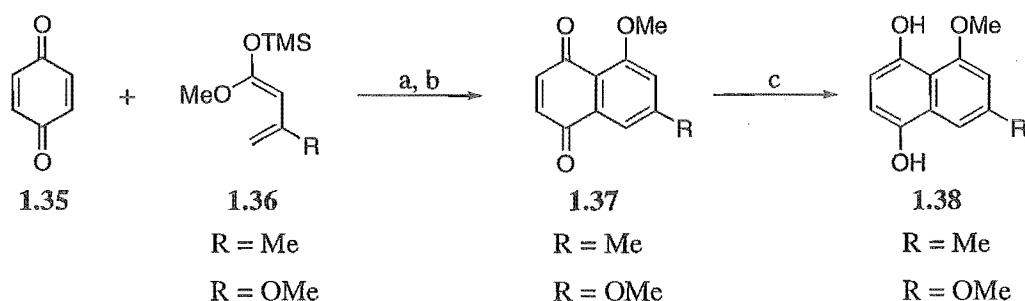


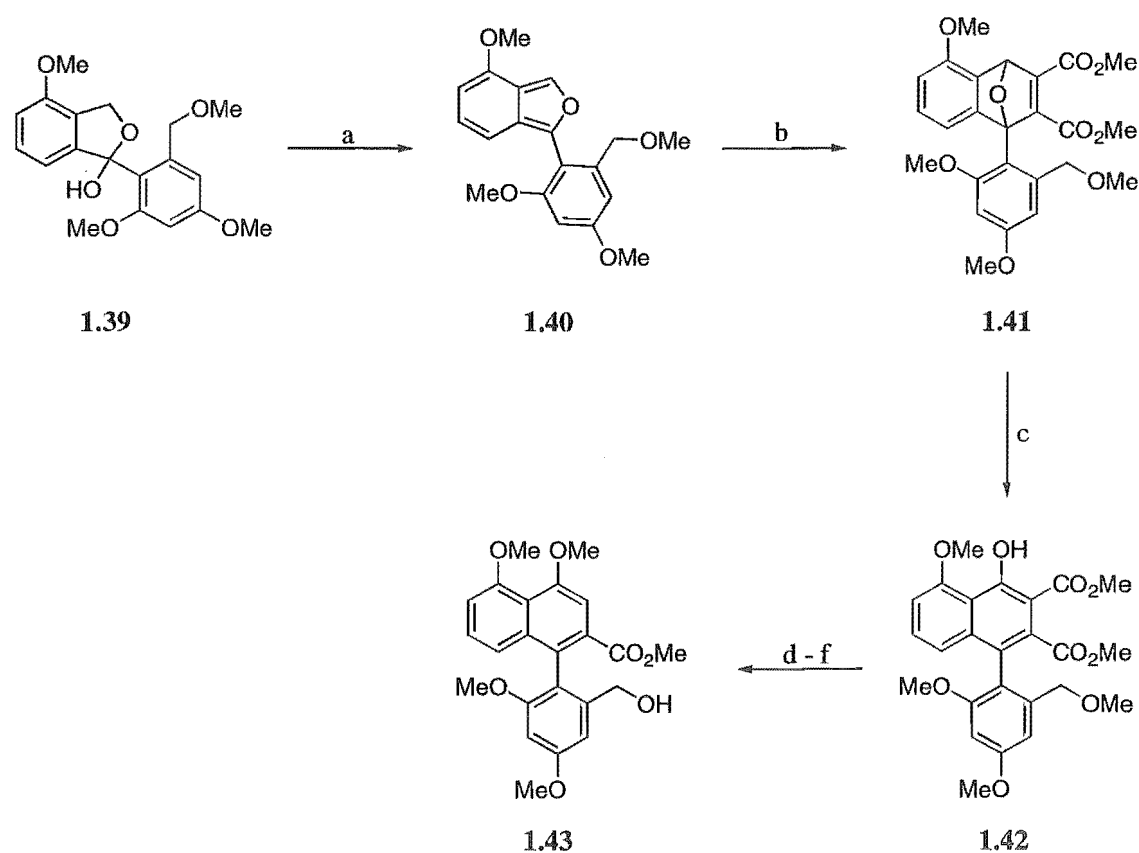
Figure 1.5 Products from Hoye's benzyne reaction.

The Diels-Alder reaction, using an appropriately functionalised quinone as the dienophile, has also been used to construct the naphthalene entity (**Scheme 1.7**). For example, Zhang *et al* prepared a variety of naphthalene precursors by cyclisation of 1,4-benzoquinone (**1.35**) with the dienes **1.36**, following which, treatment with acetic acid gave the naphthoquinones **1.37**.^{8c} Reduction with sodium dithionite gave naphthalenes **1.38**. The naphthalenes generated by this highly efficient procedure were subsequently utilised in the preparation of structural analogues of the Michellamine natural products.^{8c} Although useful for the synthesis of trioxxygenated naphthalenes, this chemistry would be difficult to utilise in a synthesis of 1,8-dioxygenated naphthalenes as an unsymmetrical dienophile would be required. This would introduce problems associated with the formation of regioisomers and as a result lower the efficiency of such a process.



Scheme 1.7 Reagents and yield: (a) CH_2Cl_2 , reflux; (b) HOAc; (c) $\text{Na}_2\text{S}_2\text{O}_4$, $\text{H}_2\text{O}/\text{EtOAc}$, 100 % over 3 steps.

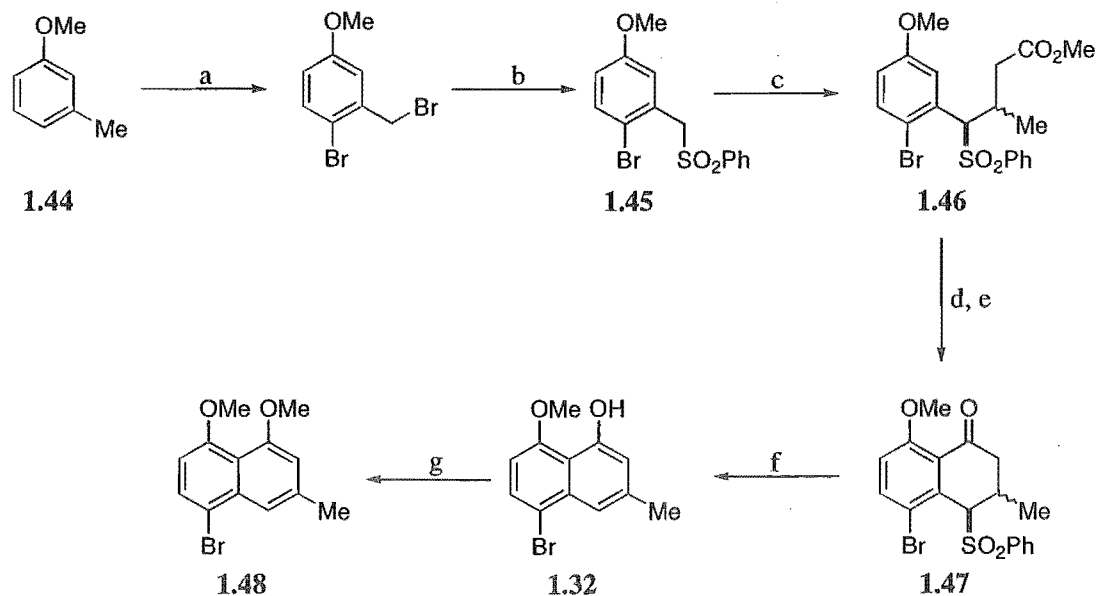
A synthesis of aryl-substituted naphthalenes was reported in Epszajn *et al.*'s study on *ortho*-aromatic metalation (**Scheme 1.8**).¹⁹ Treatment of the phthalan **1.39** with catalytic TFA and trapping of the resulting isobenzofuran **1.40** with dimethyl acetylenedicarboxylate ($\text{MeO}_2\text{C}\equiv\text{CCO}_2\text{Me}$) gave the adduct **1.41**. The naphthalene framework **1.42** was obtained by treatment of **1.41** with TsOH and this intermediate could be converted into alcohol **1.43**, a precursor to the naphthylisoquinoline alkaloids, by a series of functional group manipulations. The yields are somewhat low in this sequence and this, coupled with the multi-step procedure for preparation of the starting material, somewhat limits this approach.



Scheme 1.8 Reagents and yields: (a) cat. $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 ; (b) $\text{MeO}_2\text{C}\equiv\text{CCO}_2\text{Me}$, CH_2Cl_2 ; (c) cat. TsOH, toluene, 24 % over 3 steps; (d) HBr, H_3PO_2 , HOAc, 33 %; (e) MeI, K_2CO_3 , acetone, 60 %; (f) MeOH, cat. DOWEX®, 55 %.

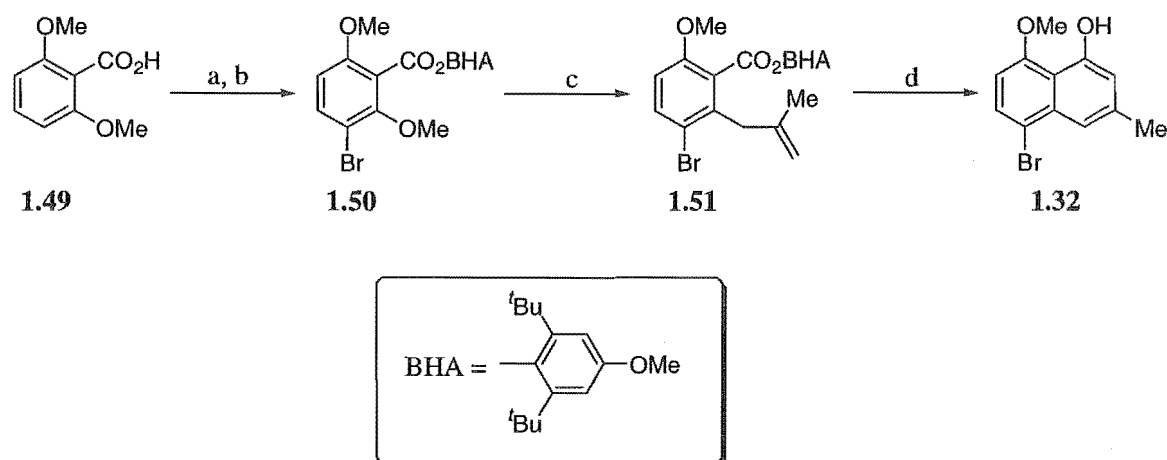
1.2.2.2 Intramolecular Cyclisations

Due to the cumbersome chromatographic purification of the material obtained by Hoyer *et al.*'s earlier procedure (Figure 1.5), they subsequently developed an alternative route to the desired naphthol **1.32** (Scheme 1.9).²⁰ This seven-step sequence began with bis-bromination of *meta*-methylanisole (**1.44**). Addition of sodium benzenesulfinite gave the desired sulfone **1.45** in excellent yield. Deprotonation and addition of methyl crotonate resulted in the formation of a diastereoisomeric mixture of sulfones **1.46**. Hydrolysis of the ester group, followed by cyclisation with TFA gave the ketosulfones **1.47**. Elimination of the sulfone group using potassium *t*-butoxide yielded the naphthol **1.32**. Finally, methylation gave the desired naphthalene building block **1.48**. The yields are good for this sequence and as many crystalline intermediates are involved, chromatography can be avoided. However, it was noted that while on one occasion this sequence was successfully applied to the corresponding MOM-protected naphthol (**1.32** MOM instead of Me), it was found that the acid-catalysed cyclisation to give the ketosulfones was not reproducible. This has limited the application of this sequence for preparing other substituted naphthalenes.



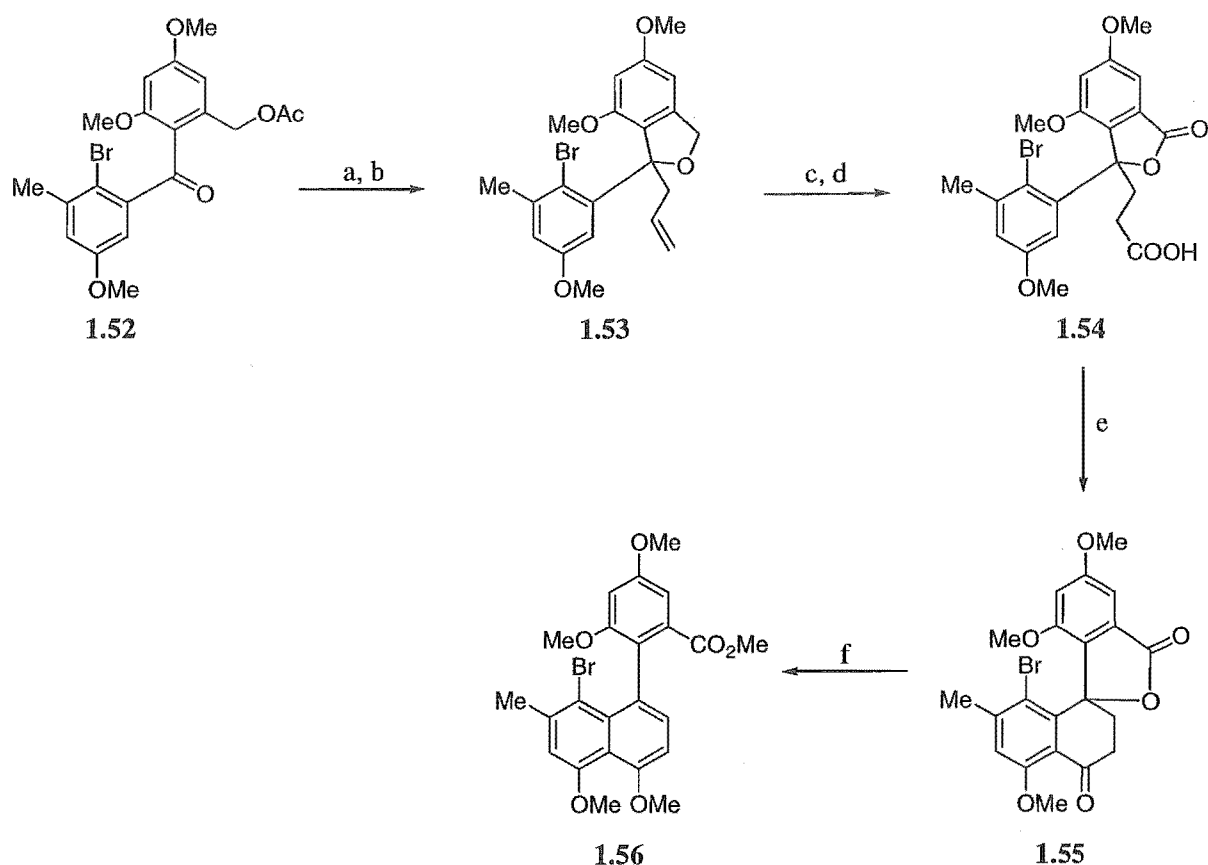
Scheme 1.9 Reagents and yields: (a) NBS, $h\nu$, CH₂Cl₂, 88 %; (b) NaSO₂Ph, DMF, 95 %; (c) LDA, methyl crotonate, THF, 86 %; (d) KOH, MeOH, 100 %; (e) TFA, 1,2-dichloroethane, 87 %; (f) KO^tBu, THF, 92 %; (g) Me₂SO₄, Bu₄NBr, CH₂Cl₂, 94 %.

During their investigations into the accelerating effects of *meta*-substituents in ester-mediated nucleophilic aromatic substitution (S_NAr) reactions, Hattori *et al* synthesised naphthol **1.32** (Scheme 1.10).²¹ Previously, they had shown that the highly hindered 2,6-di-*t*-butyl-4-methoxyphenyl (BHA) ester group activates an *ortho*-alkoxy substituent for S_NAr . As they are easily removed, esters make useful alternatives to the usual oxazoline functionality required in the conventional Meyer's reaction. Thus, esterification of the acid **1.49**, followed by bromination, yielded the bromoester **1.50**. Treatment with 2-methylprop-2-enylmagnesium chloride gave monoallylated product **1.51**, which upon reaction with sodium methoxide in HMPA gave the desired naphthol **1.32**. The solvent used for this reaction is both expensive and toxic however, the authors commented that studies were being undertaken to find a more convenient alternative solvent for the final cyclisation.



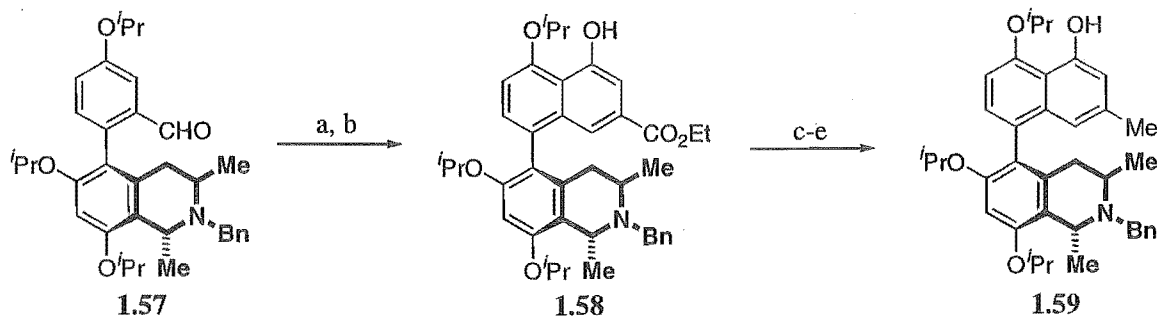
Scheme 1.10 Reagent and Yields: (a) 2,6-di-*tert*-butyl-4-methoxyphenol, TFAA, C_6H_6 , 93 %; (b) Br_2 , AcOH, 86 %; (c) Mg, 3-chloro-2-methylpropene, THF, 84 %; (d) NaOMe, HMPA, 73 %.

Rao *et al* annealed the naphthalene ring onto a benzophenone derivative (Scheme 1.11).¹⁵ Addition of allylmagnesium bromide to ketone **1.52** gave, after trapping of the intermediate diol, the *iso*-benzofuran **1.53**. Hydroboration-oxidation, followed by Jones oxidation, gave the acid lactone **1.54**. Cyclisation using polyphosphate ester (PPE) afforded the tetralone **1.55** in 84 % yield, which readily underwent aromatisation to the substituted naphthalene **1.56** upon treatment with acidified methanol. This approach requires numerous manipulations of functionality and as such, has not been extensively utilised.



Scheme 1.11 Reagents and yields: (a) $\text{CH}_2=\text{CH}-\text{CH}_2\text{MgBr}$, THF/ether; (b) TsOH , CH_2Cl_2 , 72 % over 2 steps; (c) $\text{BH}_3\cdot\text{SMe}_2$, NaOH , H_2O_2 , THF, 78 %; (d) Jones's reagent, acetone, 74 %; (e) PPE, CHCl_3 , 84 %; (f) MeOH , HCl , 80 %.

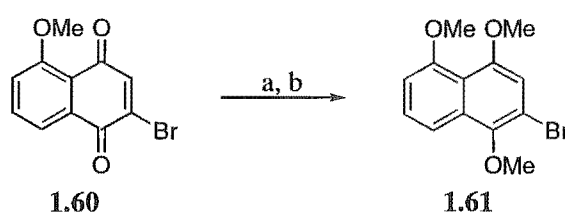
Bringmann's group have utilised a Stobbe-type reaction for construction of the naphthalene portion of korupensamine B (**Scheme 1.12**).²² Reaction of the ester enolate of diethyl succinate with biaryl aldehyde **1.57**, followed by ring closure, gave naphthylisoquinoline **1.58**. A reduction-bromination-reduction sequence gave the desired naphthol **1.59**, which could then be converted into the natural product korupensamine B.



Scheme 1.12 Reagents and yields: (a) $(\text{CH}_2\text{CO}_2\text{Et})_2$, NaOEt ; (b) Ac_2O , 52 % over 2 steps; (c) LiAlH_4 , 72 %; (d) PPh_3 , $(\text{Br}-\text{CCl}_2)_2$; (e) LiAlH_4 , 96 % over 2 steps.

1.2.2.3 Other Approaches

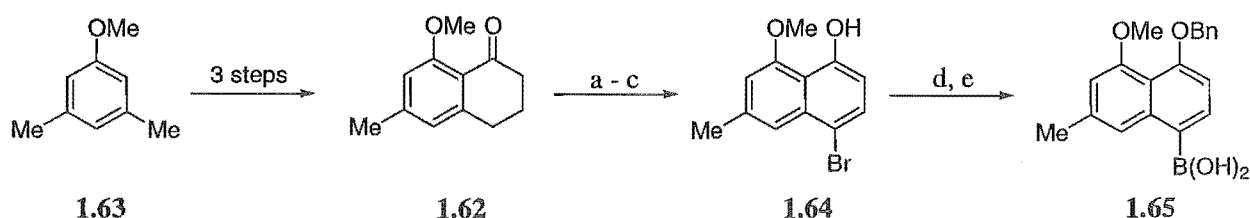
Rizzacasa and Sargent utilised the bromoquinone **1.60** in their approach to the naphthalene moiety.²³ Reduction with sodium dithionite, followed by methylation, gave the appropriately functionalised naphthalene **1.61**, which was used for preparation of precursors for a Meyer's biaryl coupling (Figure 1.6).



Reagents and yield: (a) $\text{Na}_2\text{S}_2\text{O}_4$; (b) Me_2SO_4 , NaOH , Bu_4NBr , $\text{H}_2\text{O/ether}$, 73 %.

Figure 1.6 Rizzacasa and Sargent's naphthalene synthesis.

In their naphthalene synthesis Dawson *et al* utilised the tetralone **1.62** prepared from 3,5-dimethylanisole (**1.63**) (Scheme 1.13).²⁴ Aromatisation was achieved by an α -bromination/dehydrobromination sequence, following which *para*-bromination gave the naphthol **1.64**. Benzylation, followed by conversion to the boronic acid, gave the appropriately functionalised naphthalene **1.65**, for use in a palladium-catalysed biaryl coupling.²⁵



Scheme 1.13 Reagents and yields: (a) $\text{Me}_3(\text{C}_6\text{H}_5)\text{NBr}_3$, THF, 92 %; (b) DBU, CH_2Cl_2 , 95 % (c) $(n\text{-Bu})_4\text{NBr}_3$, CHCl_3 , 75 %; (d) BnBr , K_2CO_3 , 89 %; (e) $n\text{-BuLi}$, $\text{B}(\text{O}^i\text{Pr})_3$, THF, NH_4Cl , 70 %.

It is evident that a number of methods exist for construction of the naphthalene portion of the naphthylisoquinoline alkaloids. However, few of these methods have proved to be widely applicable in terms of their tolerance of functionality, such as protecting groups, and also in their flexibility in terms of positions that can be functionalised. Accordingly, development of a new

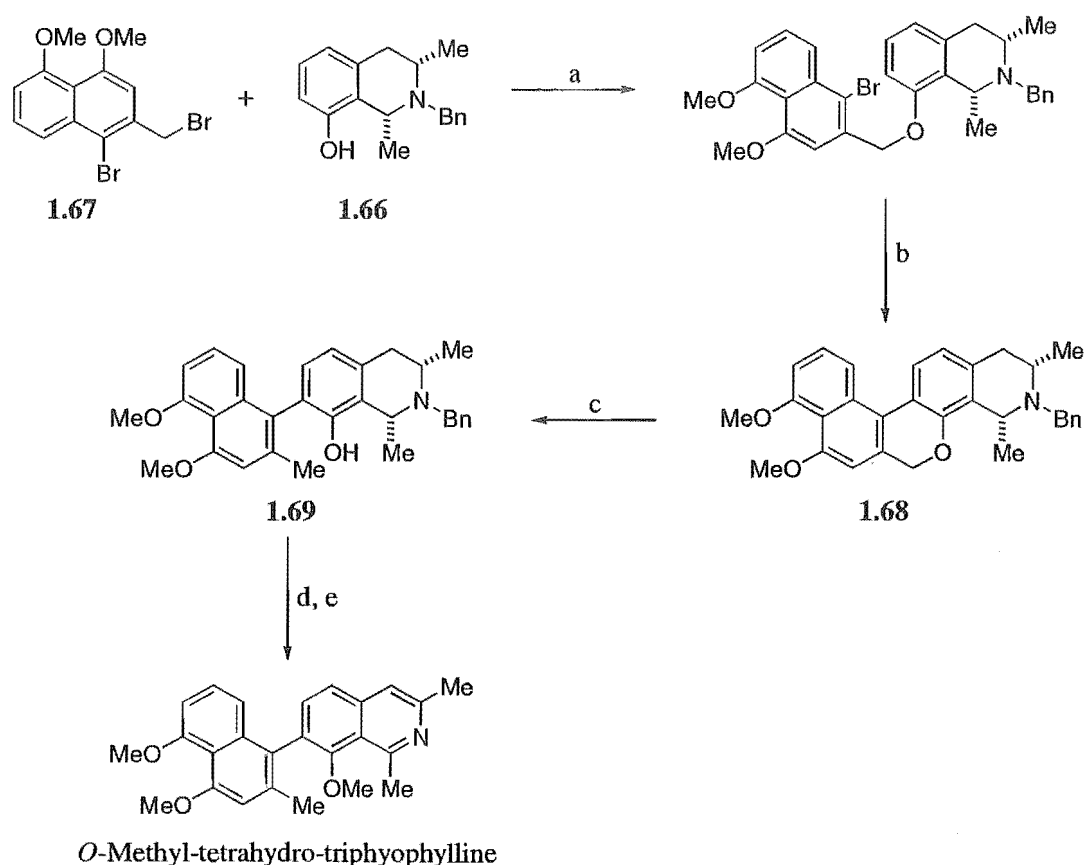
naphthalene synthesis is of importance. In order for a new synthesis to be useful it should proceed *via* intermediates which would allow flexibility in the introduction of functionality, in particular at positions that are substituted with respect to the naphthylisoquinoline alkaloid natural products.

1.2.3 Formation of the Biaryl Bond

Due to the highly hindered biaryl bonds present in these molecules, which results in atropisomers being formed, any method used to construct such a linkage should have the potential to be adapted to allow an asymmetric synthesis. Many such reactions have been investigated in the context of the total synthesis of the naphthylisoquinoline alkaloids, beginning with development of the bond-forming conditions, and culminating in selective atropisomer syntheses. What follows is by no means a comprehensive review of such reactions. The purpose is to give an overview for how such reactions are developed, in terms of the initial non-stereoselective bond forming conditions, followed by application to a successful stereoselective synthesis.

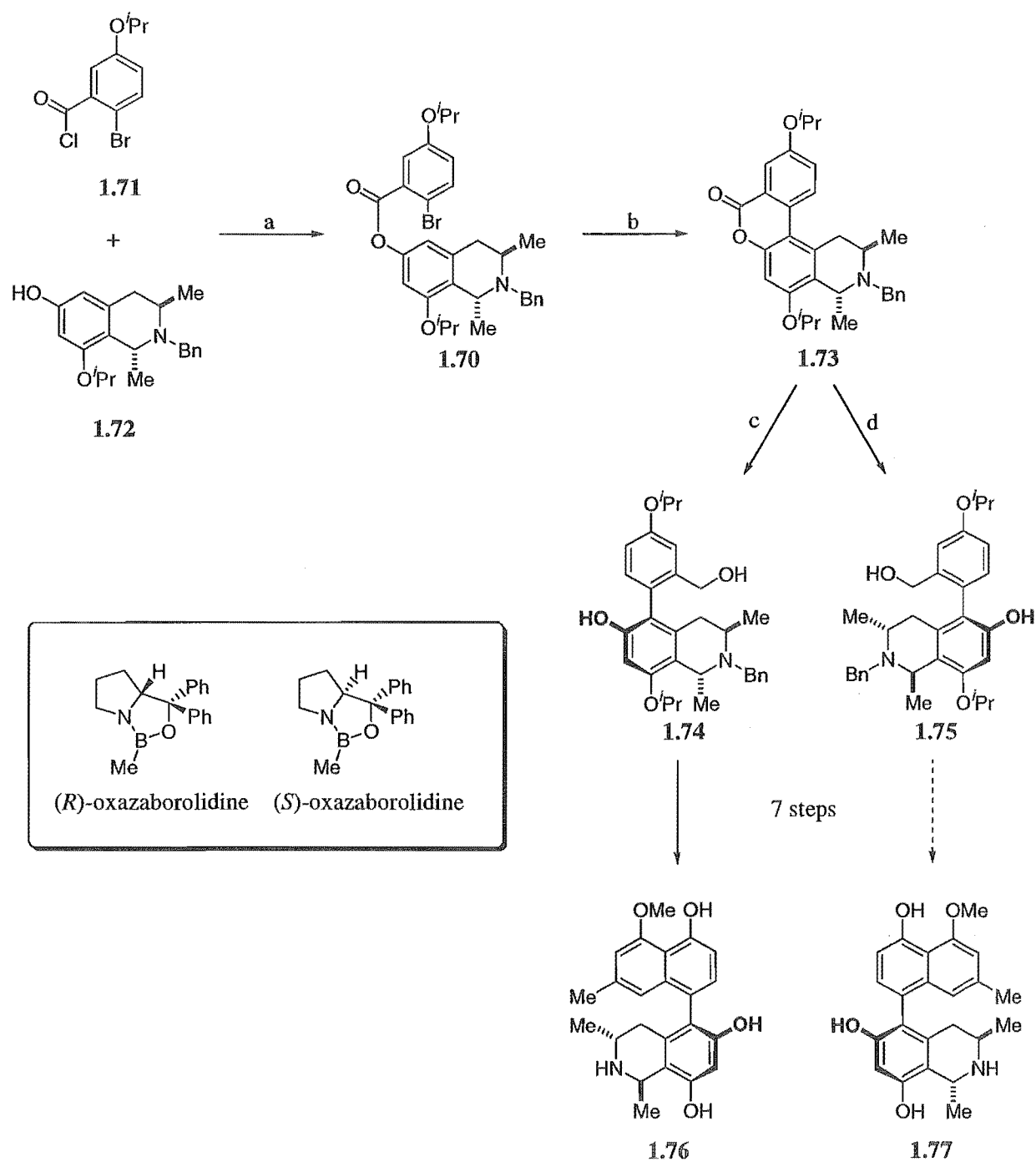
1.2.3.1 Intramolecular Approaches

In the first total synthesis of a naphthylisoquinoline alkaloid Bringmann *et al* utilised an intramolecular *ortho*-selective biaryl coupling in the preparation of *O*-methyl-tetradehydro-triphyphylline (Scheme 1.14).²⁶ Prefixation of the two moieties was carried out by *O*-alkylation of phenol **1.66** with bromide **1.67**. Biaryl bond formation was induced by photolysis, to give ether **1.68**. Reductive ring opening gave biaryl **1.69**, which was readily converted into the racemic natural product.



Scheme 1.14 Reagents and yields: (a) $\text{BnN}(n\text{-Bu})_3\text{Br}$, CH_2Cl_2 , 1M NaOH, 93 %; (b) $h\nu$ (254 nm), NEt_3 , 15 %; (c) $\text{Li}/(\text{C}_6\text{H}_5)_2$, THF, 78 %; (d) 10 % Pd/C, *trans*-decalin, reflux, 69 %; (e) $\text{BnN}(n\text{-Bu})_3\text{Br}$, Me_2SO_4 , CH_2Cl_2 , 1M NaOH, 86 %.

The low yield of the biaryl bond forming step in the above scheme prompted the emergence of the ‘Lactone Methodology’ as a tool in naphthylisoquinoline alkaloid synthesis. This concept allows diastereoselective syntheses and hinges upon formation of a lactone-bridged intermediate, which can be cleaved to give either atropisomer stereoselectively. This has led to the syntheses of 7-1’,²⁷ 5-1’,^{4h,12} and 5-8’,²⁸ linked naphthylisoquinoline alkaloids. These syntheses can be exemplified by the total synthesis of korupensamine B (Figure 1.7). Requisite ester 1.70 is prepared by reaction of acid chloride 1.71 with phenol 1.72. Intramolecular biaryl bond formation was carried out under palladium catalysis to give biaryl lactone 1.73. Stereoselective ring cleavage utilising a chiral oxazaborolidine-borane reagent allowed either configurationally stable atropisomer to be selectively generated. Biaryl 1.74 was then converted into the natural product korupensamine B 1.76, and, in principle, atropisomer 1.75 could be converted into korupensamine A 1.77.

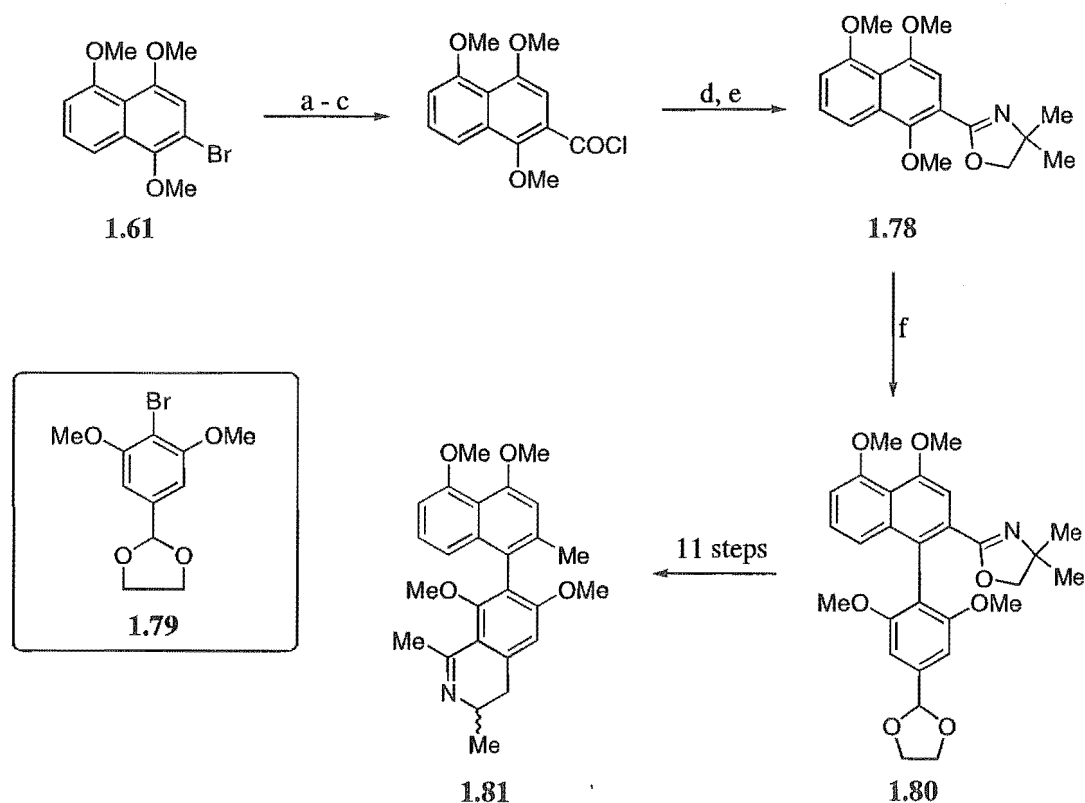


Reagents and yields: (a) NEt_3 , 74 %; (b) 10 mol % $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tolyl})_3$, N,N -dimethylacetamide, 74 %; (c) (*R*)-oxazaborolidine, BH_3 ; (d) (*S*)-oxazaborolidine, BH_3 .

Figure 1.7 Stereoselective synthesis of korpensamines A and B.

1.2.3.2 Non Transition-metal Type Intermolecular Approaches

In an intermolecular bond forming process, Sargent and Rizzacasa utilised a Meyer's biaryl-coupling in their synthesis of dehydroancistrocladisine (**Figure 1.8**).²³ The key step utilises an oxazoline to activate an *ortho*-methoxy substituent to nucleophilic aromatic substitution by an aryl Grignard reagent. Requisite oxazoline **1.78** was prepared from bromide **1.61**. Displacement of the *ortho*-methoxy group of this oxazoline, with the Grignard reagent derived from bromide **1.79**, gave biaryl **1.80** in good yield. The remaining portion of the heterocyclic ring was assembled to give ancistrocladisine **1.81** as a racemic mixture of atropisomers.

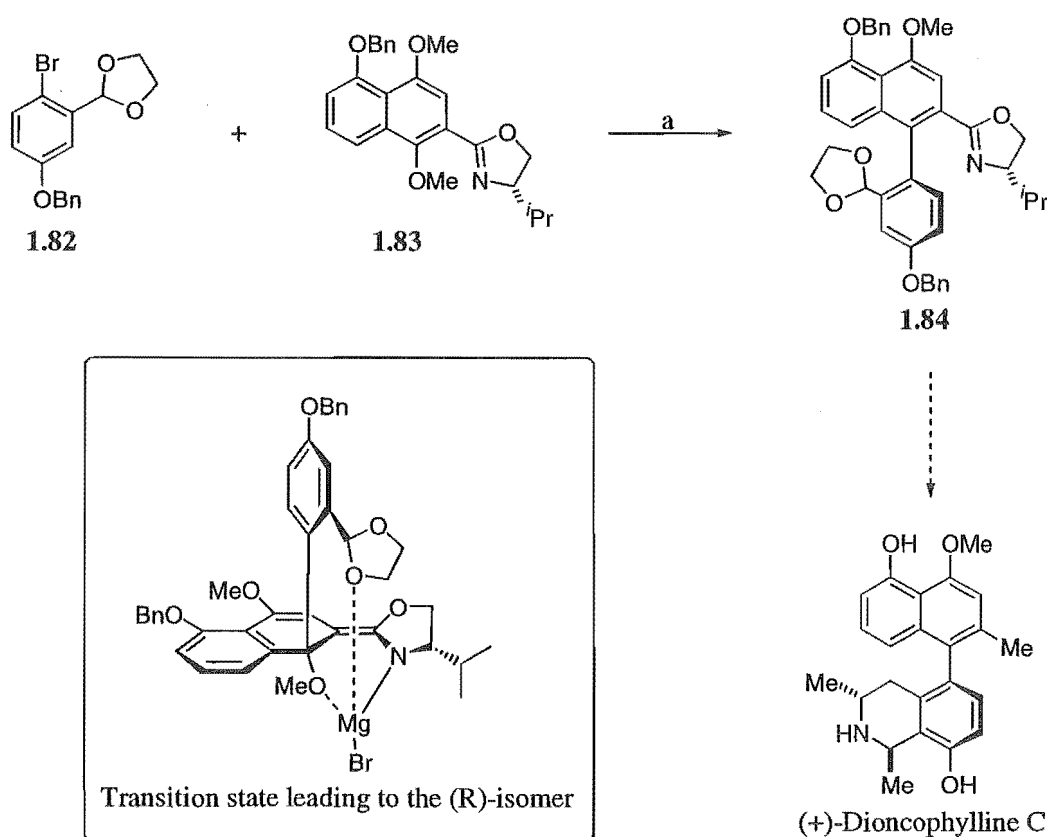


Reagents and yields: (a) CuCN , DMF, 94 %; (b) KOH , $\text{MeOH}/\text{H}_2\text{O}$, 100 %; (c) $(\text{COCl})_2$, CH_2Cl_2 ; (d) $\text{HOCH}_2\text{CMe}_2\text{NH}_2$, CH_2Cl_2 ; (e) SOCl_2 , CH_2Cl_2 , 85 %; (f) Mg , **1.77**, THF, reflux, 81 %.

Figure 1.8 Synthesis of racemic ancistrocladisine.

This methodology was extended to incorporate chiral oxazolines which has led to asymmetric syntheses of 5-1²⁹ and 7-1³⁰ *Ancistrocladus* alkaloids, with the synthesis of a biaryl precursor to

(+)-dioncophylline C being the most recent example (Figure 1.9).³¹ Reaction of the Grignard reagent, derived from bromide **1.82**, with the chiral oxazoline **1.83** gave the desired biaryl **1.84**, in 70 % yield, as a 91:9 mixture of atropisomers, favouring the (*M*)-isomer. The preference for the (*M*)-isomer was rationalised in terms of chelation control. Chelation of one of the dioxolane oxygen atoms to magnesium results in the transition state depicted below, which, after expulsion of MeOMgBr, gives the desired atropisomer. Biaryl **1.84** could then be converted into the natural product using the previously published procedures for removal of the oxazoline and assembly of the tetrahydroisoquinoline ring, however this was not carried out.

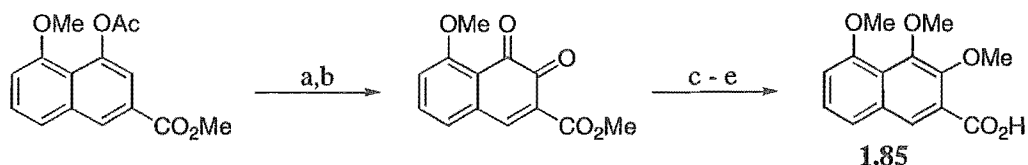


Reagents and yield: (a) Mg, THF, 70 %.

Figure 1.9 A synthetic approach to (+)-dioncophylline C.

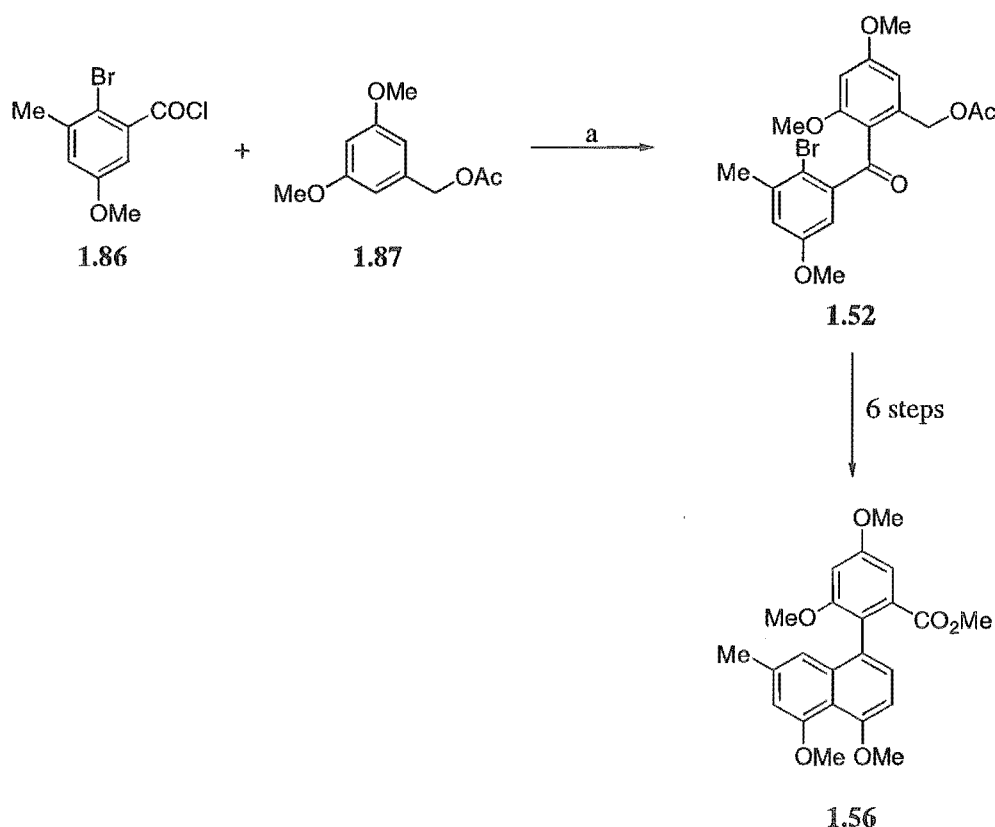
Sargent *et al* attempted to apply this methodology to the synthesis of the 7-3'-linked naphthylisoquinoline alkaloids.³² The naphthalene precursor **1.85** was prepared and converted into the desired oxazoline, but unfortunately the *ortho*-methoxy group proved inert to

displacement by Grignard reagents. This is believed to be a consequence of bond fixation in the naphthalene nucleus (**Scheme 1.15**).



Scheme 1.15 Reagents and yields: (a) NaOMe, MeOH, 96 %; (b) benzene selenic anhydride, THF, 95 %; (c) $\text{Na}_2\text{S}_2\text{O}_4$, $\text{CHCl}_3/\text{H}_2\text{O}$; (d) CH_3I , K_2CO_3 , DMF, 86 %; (e) NaOH, MeOH/ H_2O , 94 %.

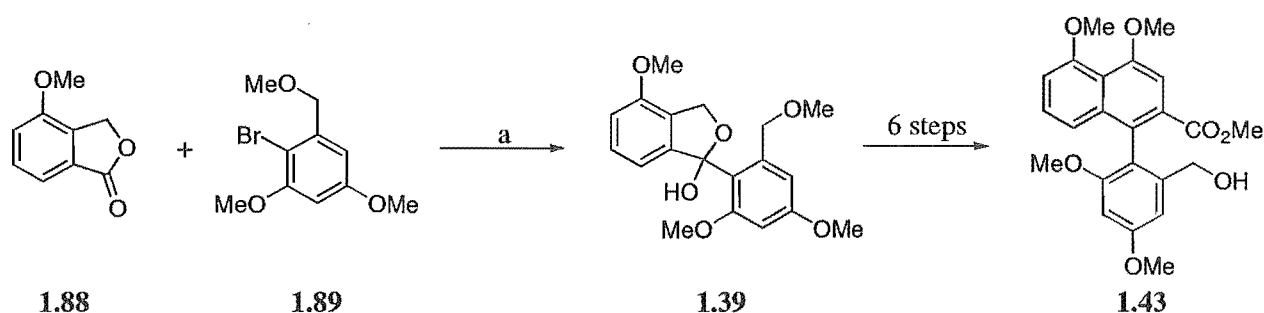
In their approach to the syntheses of *O,O,O*-trimethylkorupensamines A and B, Rao *et al* opted to form the biaryl bond early in the synthesis (**Figure 1.10**).¹⁵ Acid chloride **1.86** and 3,5-dimethoxybenzyl acetate **1.87** were coupled, in the presence of AlCl_3 , to give benzophenone **1.52**. The naphthalene ring was assembled, as detailed in **Scheme 1.11**, to give biaryl **1.56**. The remainder of the synthesis, including separation of the resulting atropisomers, is as detailed in **Scheme 1.5**.



Reagents and yields: (a) AlCl_3 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, 72 %.

Figure 1.10 Rao's biaryl bond forming reaction.

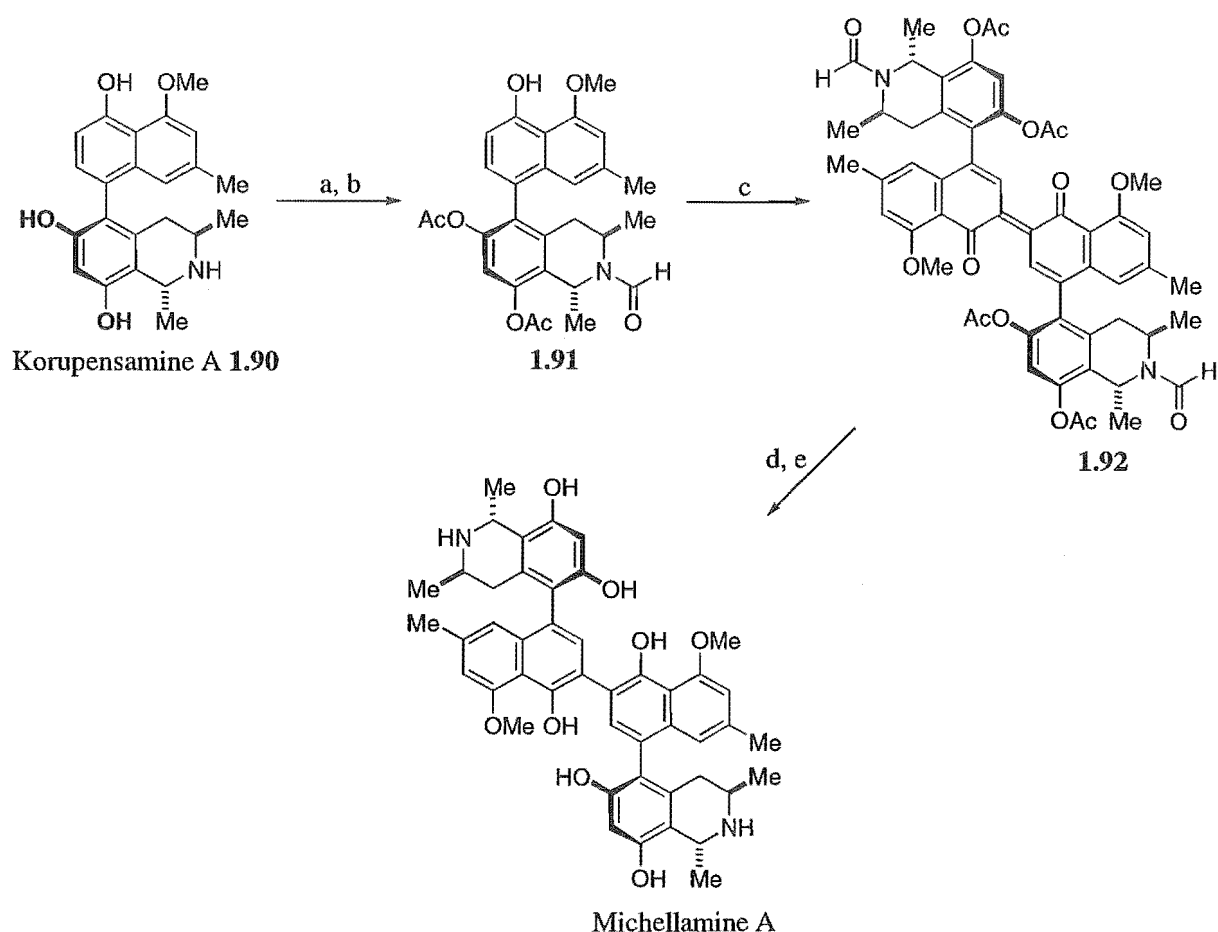
In their studies into the application of organolithium-related reagents in organic synthesis, Epszajn *et al* formed a 5-1' biaryl bond as detailed in **Figure 1.11**.¹⁹ Reaction of phthalide **1.88** with the lithium species, derived from bromide **1.89**, gave the phthalan **1.39**. Annulation of the naphthalene ring, as described in **Scheme 1.8**, gave the arynaphthalene **1.43**, a precursor of the naphthylisoquinoline alkaloids. However, this approach has not been utilised in a total synthesis thus far.



Reagents and conditions: (a) n-BuLi, THF.

Figure 1.11 Synthesis of a naphthylisoquinoline alkaloid precursor.

Bringmann *et al* described a 'Biomimetic' oxidative dimerisation to form the biaryl bond in the first total synthesis of michellamines A, B, and C (**Scheme 1.16**).³³ Korupensamine A **1.90**, a natural product co-occurring with the michellamines, was protected in order to prevent other undesirable oxidative coupling reactions. Subsequent dimerisation of monophenolic oxidative coupling precursor **1.91** with silver(I) oxide gave the binaphthylidendione **1.92** which, upon reduction and deprotection, gave michellamine A. Other groups in their syntheses of michellamine alkaloids,^{18, 34} and related analogues,^{4c,4h,4k,35} have also used oxidative couplings to form the desired biaryl bonds. This has emerged as an important reaction as it is found that the dimers formed often exhibit improved, or different biological activities in comparison to their monomeric precursors.⁹



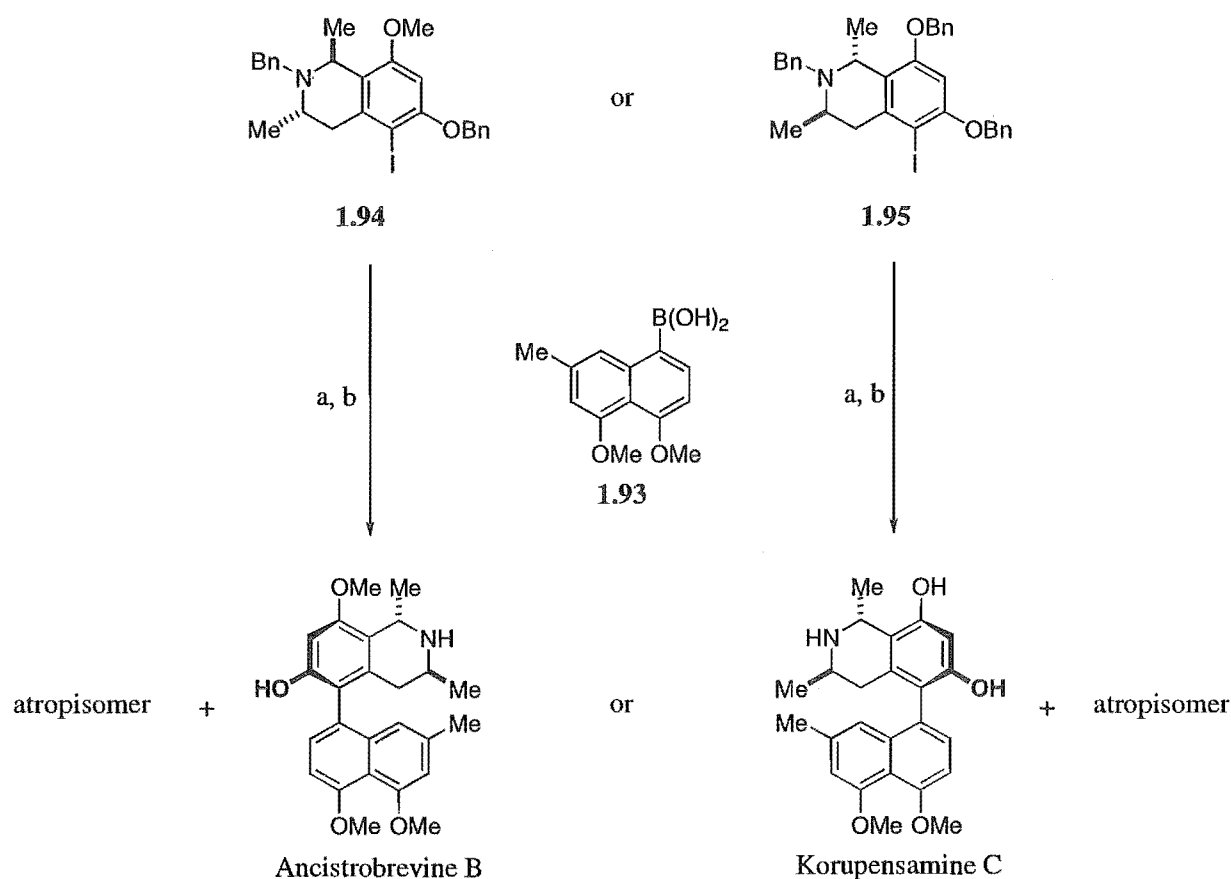
Scheme 1.16 Reagents and yields: (a) $(\text{CH}_3)_3\text{CO}_2\text{CHO}$, CH_2Cl_2 ; (b) CH_3COCl , NEt_3 , DMAP, CH_2Cl_2 , 90 %; (c) Ag_2O , NEt_3 , CHCl_3 , 85 %; (d) NaBH_4 , *i*-PrOH; (e) MeOH, HCl, 67 %.

1.2.3.3 Transition Metal-catalysed Intermolecular Approaches

With the advent of transition metal-catalysed biaryl coupling methodology, many elegant syntheses of michellamine^{27,34a,36} and related alkaloids³⁷ have been completed using this concept to form the biaryl bonds. The major advantage is the ability to directly couple the naphthalene and heterocyclic portions together. Selections of syntheses have been chosen to demonstrate the utility of such chemistry.

Hoye and Chen conducted some preliminary studies on the palladium-catalysed cross-coupling reaction to form highly hindered biaryls.³⁸ They found that Suzuki coupling was the most effective and subsequently used this reaction in synthesis of ancistrobrevine C and

korupensamine C (Figure 1.12). Coupling of naphthalene 1.93 with either tetrahydroisoquinoline fragments 1.94 or 1.95 gave mixtures of atropisomers which, upon deprotection, were separated by HPLC to give the natural products korupensamine C and ancistrobrevine B respectively.³⁹



Reagents and yield: (a) cat. $\text{Pd}(\text{PPh}_3)_4$, 1.93, sat'd NaHCO_3 , toluene, 71 - 76 %; (b) Pd/C , H_2 , MeOH , CH_2Cl_2 , 100 %.

Figure 1.12 Suzuki coupling to give korupensamine A and ancistrobrevine B.

Again, the issue regarding stereocontrol in the formation of the biaryl axis arises. Recently, some novel approaches have emerged with regards to the stereoselective biaryl coupling of the two molecular entities. The first of these works utilised 'hydroxyl handles' on each of the coupling participants.¹⁴ Coupling of these molecules under standard Suzuki conditions revealed only a slight preference for the (*P*)-isomer, which was attributed to steric effects. In contrast, coupling utilising an internal chelating phosphane ligand proved far more rewarding, affording a

single diastereoisomer in 81 % yield. The sole formation of (*P*)-isomer **1.96** was attributed to the geometry of the transition state leading to the reductive elimination of the product. It was proposed that the PPh_2 -substituted benzoate residue is best suited with the phosphorous coordinated to the bottom of the palladium, relative to the plane of the tetrahydroisoquinoline ring. If this arrangement is favoured, then the phenyl groups on the phosphorus, as well as the phenyl ring on the ester, block the back and underside, forcing the bulky naphthalene portion to protrude over the tetrahydroisoquinoline ring. Subsequent reductive elimination would then give the observed atropisomer (**Figure 1.13**).

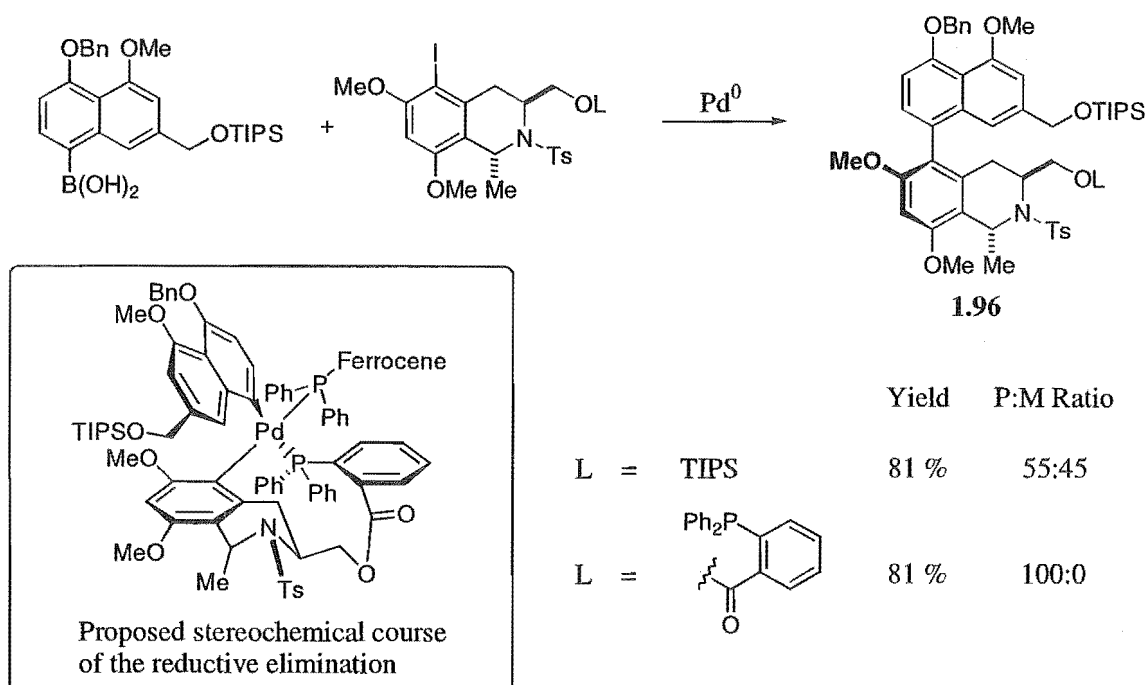
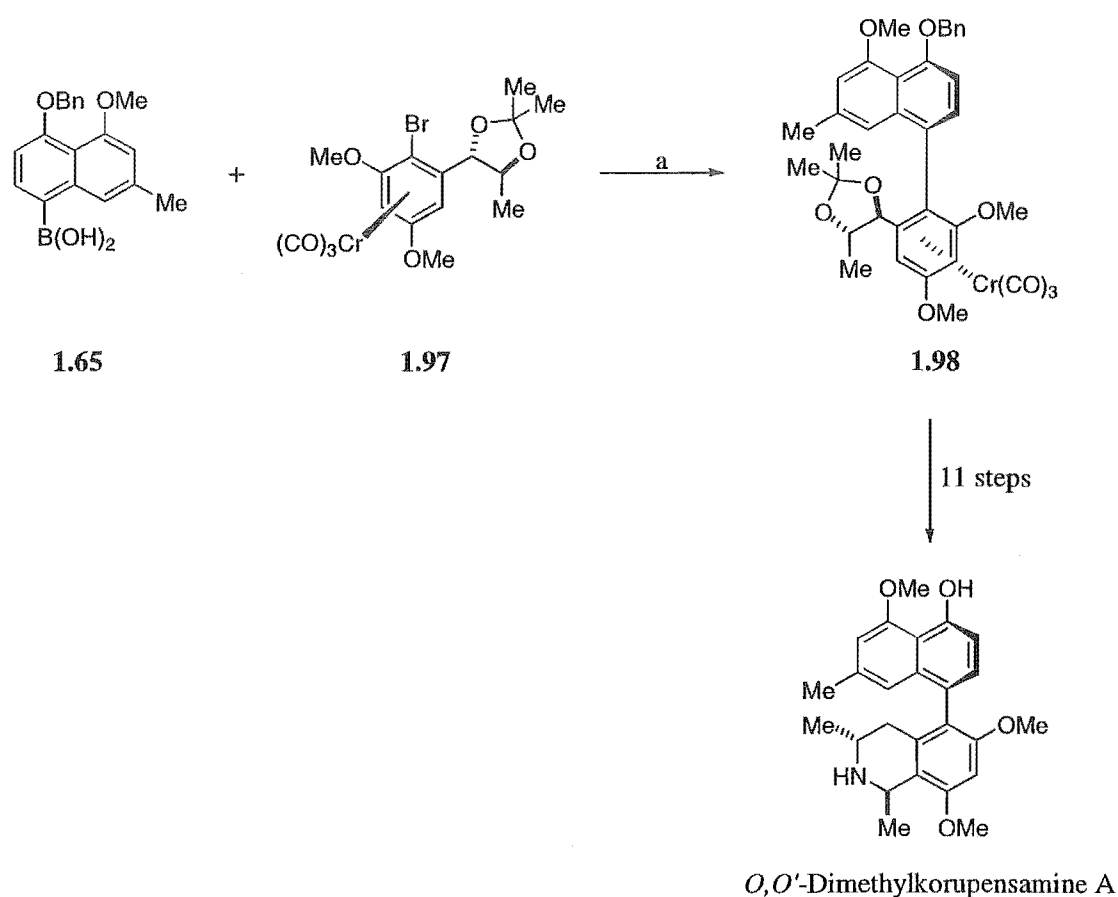


Figure 1.13 Stereoselective biaryl coupling.

In their stereoselective synthesis of *O,O'*-dimethylkorupensamine A, Uemura *et al* utilised a planar chiral arene-chromium complex in order to control the formation of the biaryl bond (**Scheme 1.17**).¹⁶ Coupling of chiral planar chromium complex **1.97** with boronic acid **1.65** gave the biaryl **1.98** as a single atropisomer in excellent yield. Subsequent assembly of the heterocyclic moiety gave *O,O'*-dimethylkorupensamine A, as described in **Scheme 1.6**.



Scheme 1.17 Reagents and yields: (a) 5 mol % $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , $\text{MeOH}/\text{H}_2\text{O}$, 90 %.

Upon examination of the aforementioned synthetic work carried out in the area of naphthylisoquinoline alkaloid synthesis, it is evident that these natural products are worthy synthetic targets and they have been the catalysts for a great deal of innovative research. Many advances in the area of synthetic chemistry have been achieved as a result of tackling these challenging natural products. Researchers have been forced to investigate new methods for naphthalene synthesis, heterocycle synthesis, and biaryl bond formation.

1.3 Work Described in this Thesis

In addition to the natural products discussed above, there is another class of compounds that have a rare 7-3' biaryl linkage (Figure 1.14). The only two members of this group isolated thus far are ancistrocladidine **1.99** and ancistrotectorine **1.100**.

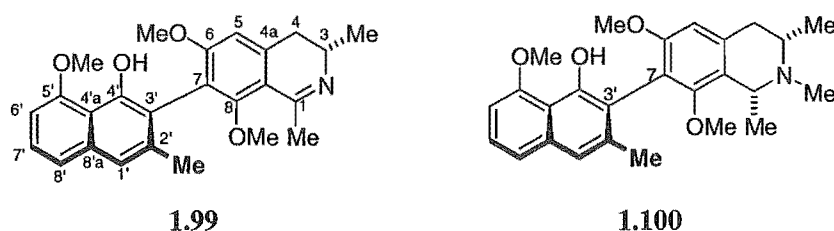


Figure 1.14 7-3'-Linked Naphthylisoquinoline alkaloids.

Ancistrocladidine **1.99** was isolated from the roots of *Ancistrocladus heyneanus* in 1973 and the structure reported as shown above, but without the absolute configuration established.⁴⁰ Following this, the absolute configuration was determined utilising the exciton chirality method and chemical degradation.⁴¹ The proposed structure was later confirmed by X-ray diffraction.⁴² Ancistrocladidine was also recently isolated from *Ancistrocladus tectorius*, the roots of which have been used to treat dysentery and malaria, and this allowed the unambiguous assignment of the ¹H and ¹³C NMR spectra.⁴³

Analysis of the ¹H NMR spectrum of ancistrocladidine revealed a phenolic proton at δ 9.63. The ABX protons on the naphthalene nucleus at δ 7.36 (d, J = 7.3 Hz), 7.28 (t, J = 7.3 Hz), and 6.71 (d, J = 7.3 Hz) were assigned to H-8', H-7', and H-6' respectively. NOE effects were observed between a methoxy group at δ 3.99 and H-6', and between a methoxy group at δ 3.75 and H-5. The remaining methoxy signal at δ 3.37, which showed no NOE with an adjacent aromatic proton, was attributed to position 8. The resonance at δ 1.43 (d, J = 6.7 Hz) was assigned to the methyl group at position 3. This was coupled to a multiplet at δ 3.41, assigned to H-3, which itself was coupled to a pair of geminally coupled methylene protons (H-4 α and H-4 β), at δ 2.69 (dd, J = 15.5, 4.5 Hz), and δ 2.42 (dd, J = 15.5, 1.8 Hz). The multiplet at δ 3.41 was also coupled to the 1-Me group at δ 2.49 (d, J = 1.8 Hz).

In 1985 a new 7-3' linked naphthylisoquinoline alkaloid, ancistrotectorine **1.100** was reported.⁴⁴ This alkaloid has also recently been isolated from the leaves of *Ancistrocladus guineënsis*.⁴⁵ Ancistrotectorine **1.100** exhibited a similar ¹H NMR spectrum to that of ancistrocladidine **1.99**, apart from the appearance and position of the C1-methyl group, and an N-Me singlet at δ 2.48. The C1-methyl group is now coupled to H-1 and appears at δ 1.47 as a doublet ($J = 6.4$ Hz). These observations were consistent with a tetrahydroisoquinoline moiety, as opposed to the 3,4-dihydroisoquinoline moiety present in ancistrocladidine **1.99**.

Although many elegant total syntheses of naphthylisoquinoline alkaloids have been published, no total synthesis of either **1.99** or **1.100** has been reported. The 7-3'-naphthylisoquinoline alkaloids present a tremendous synthetic challenge, as they contain the most sterically congested biaryl bond within this group of natural products. Also if a synthetic approach is adopted whereby the heterocyclic moiety is assembled after the biaryl bond is formed, the formation of a mixture of atropisomers is inevitable.* This makes control of the stereochemistry of the biaryl axis a difficult prospect. The research described in this thesis deals with synthetic studies on these 7-3'-linked compounds. The initial aims of this research were as follows:

- To design and implement a new method for the synthesis of naphthalene building blocks, which allows functionality to be introduced at a variety of positions around the ring.
- To investigate the synthesis of appropriately functionalised dihydroisoquinoline precursors which, upon reaction with intermediates from the above sequence, could be used to form a 7-3' biaryl bond.
- To bring together the above goals and complete a stereoselective total synthesis of a 7-3'-linked naphthylisoquinoline alkaloid.

* See Figure 4.24 on page 118 for a pictorial representation.

Chapter Two

Synthesis of Some Useful Naphthalene Building Blocks

2.1 Introduction

As discussed in Chapter 1, the 1,8-dioxygenated-naphthalene moiety is a key constituent of the naphthylisoquinoline alkaloids. A number of methods for the construction of this component were discussed. Although valuable, many of these syntheses are not readily applicable to the synthesis of a variety of naphthalene precursors and thus, it was proposed that a new naphthalene synthesis be developed. In order for this to offer any advantages over previously described methods, the synthesis would need to be amenable to large-scale preparations, enable functionality to be introduced at a variety of positions around the ring, and ensure flexibility in the choice of a protecting group (Figure 2.1).

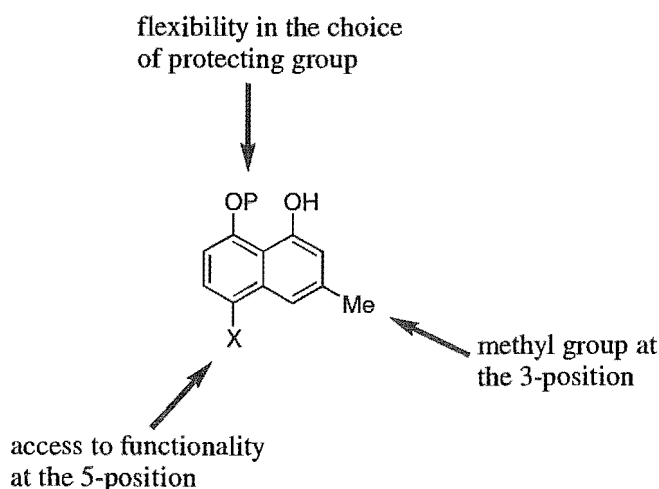


Figure 2.1 Key attributes for the design of a new naphthalene synthesis.

Wallace *et al* have shown that benzocyclobutenones are versatile precursors to substituted tetralones and naphthalenes. In their search for a route to substituted α -tetralones **2.1**, a reaction sequence where an alkenylbenzocyclobutenol **2.2** is thermally transformed into an *ortho*-quinone dimethide **2.3** was investigated.⁴⁶ Subsequent electrocyclisation, followed by quenching of the enol derivative **2.4**, with an electrophile, was expected to produce the substituted α -tetralone **2.1** (Figure 2.2).

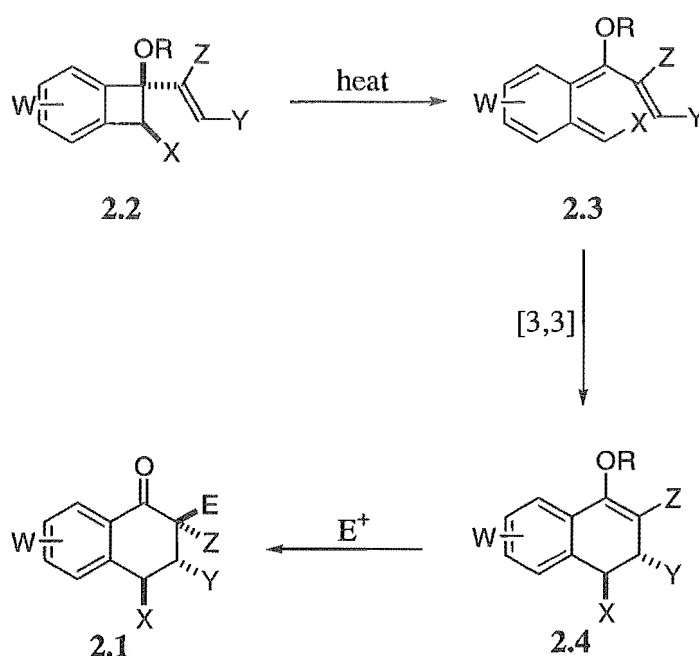


Figure 2.2 Wallace *et al*'s proposed synthesis of α -tetralones.

Initially, the reactions of some simple alkenyl Grignard reagents with 3,6-dimethoxybenzocyclobutenone (**2.5**) were studied. It was expected that *in situ* ring opening of the intermediate alkoxy species would be a potential pitfall of this approach. However, analysis of the ^1H NMR spectra of the crude Grignard addition products revealed only traces of the ring opened products **2.6**. If the benzocyclobutenols were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the ring opened species were the exclusive products. Cyclisation of the benzocyclobutenols proceeded smoothly, indicating that the *peri*-methoxy substituents did not suppress the electrocyclic ring opening reactions (**Figure 2.3**).

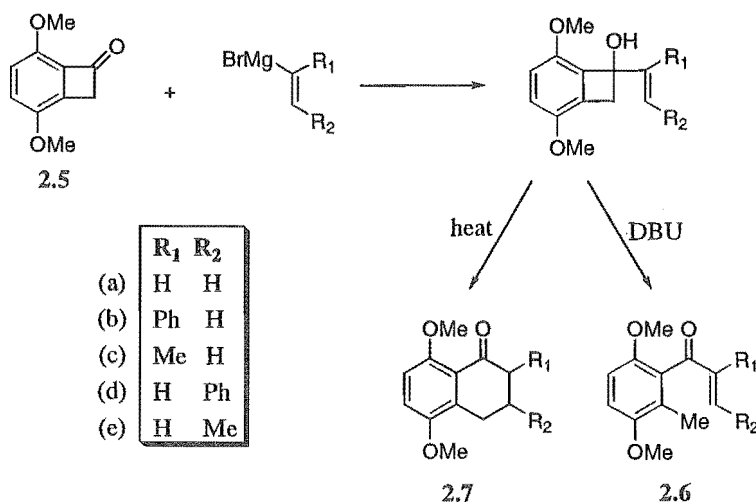


Figure 2.3 Synthesis and reactions of alkenylbenzocyclobutenols.

Alkynyllithium reagents **2.8** were also found to add cleanly to benzocyclobutenones.⁴⁶ Thermolysis of these adducts provided the naphthols **2.9** as shown in Figure 2.4.

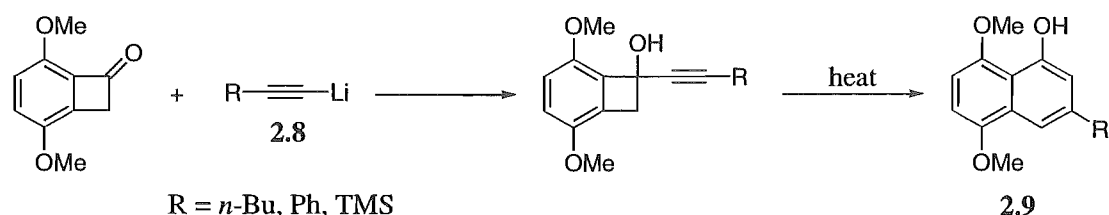


Figure 2.4 Synthesis and reaction of an alkynylbenzocyclobutenol.

It was envisaged that this strategy could be adapted to allow for the development of a synthesis of 1,8-dioxygenated naphthalenes, such as those present in the naphthylisoquinoline alkaloid class of natural products. The types of reactions and intermediates involved should allow ready variation in functionality, as well as be amenable to large-scale preparations.

Disconnection of the naphthalene core of the naphthylisoquinoline alkaloids, as below, requires access to 6-alkoxybenzocyclobutenones **2.10** (Figure 2.5).

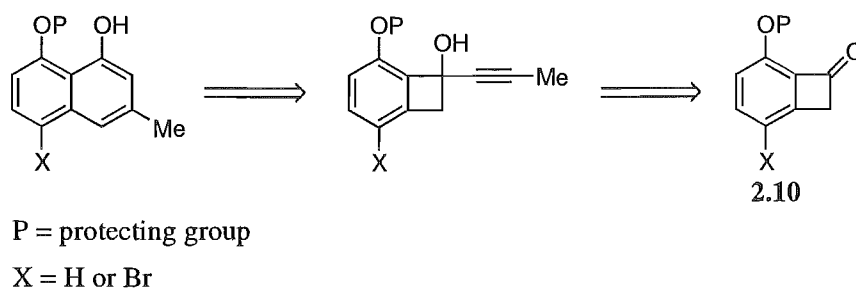


Figure 2.5 Retrosynthesis of the naphthalene core.

The most amenable approach⁴⁷ to 6-alkoxysubstituted benzocyclobutenones is a two step procedure where 3-methoxybenzyne **2.11** is reacted with either a dialkyl ketene acetal⁴⁸ or a silyl ketene acetal⁴⁹ (Figure 2.6). The product from the regioselective $[2\pi + 2\pi]$ cycloaddition is hydrolysed to give the benzocyclobutenone **2.12**.

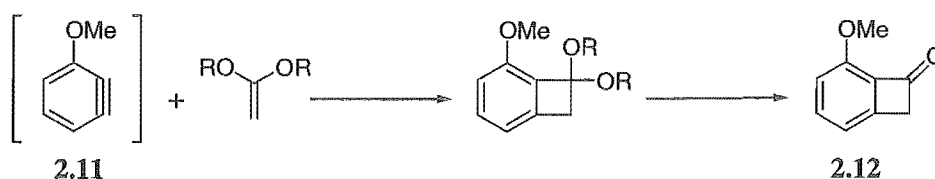


Figure 2.6 $[2\pi + 2\pi]$ Cycloaddition to produce benzocyclobutenones.

Accordingly, the efficient generation of 3-methoxybenzyne **2.11** is an important part of this approach and represents the starting point for this research.

2.2 Synthesis of 6-Alkoxybenzocyclobutenones

2.2.1 Efficient Generation of 3-Methoxybenzyne and its Application to the Synthesis of 6-Alkoxysubstituted Benzocyclobutenones

A number of procedures have been reported for the generation of 3-methoxybenzyne (**Figure 2.7**).⁵⁰ The key feature of these procedures is the elimination of an appropriate leaving group.

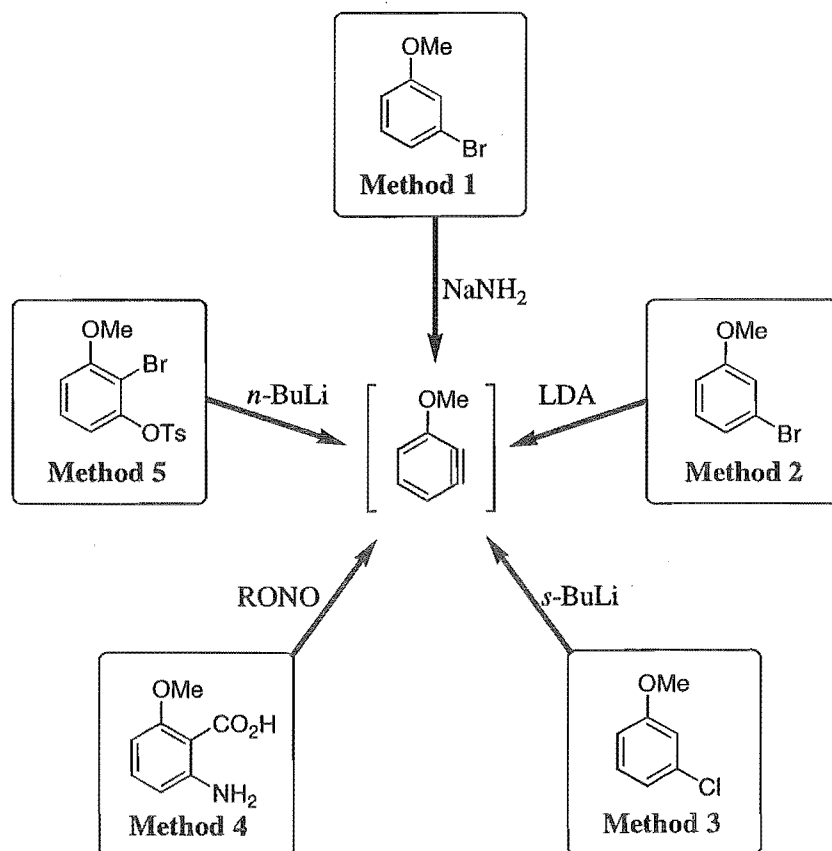
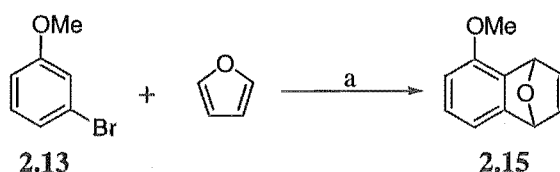


Figure 2.7 Methods for generation of 3-methoxybenzyne.

Methods 1 and 2 utilise commercially available *m*-bromoanisole **2.13** and were investigated first. The ketene acetal chosen as the partner in the $[2\pi + 2\pi]$ cycloaddition was 1,1-diethoxyethylene **2.14**, as it is readily prepared on a large scale.⁵¹

Initial work focused on repeating the procedure developed by Stevens and Bisacchi in method 1.^{48a} Treatment of *m*-bromoanisole **2.13** with commercial sodium amide, in the presence of 1,1-diethoxyethylene **2.14**, gave only recovered starting material. It has been reported that this method for benzyne generation can prove troublesome, with Liebskind's group recommending the use of freshly opened bottles of sodium amide and conducting reactions in a dry box.^{48b} As we sought a reliable method that would be amenable to large-scale preparations, alternative procedures were explored.

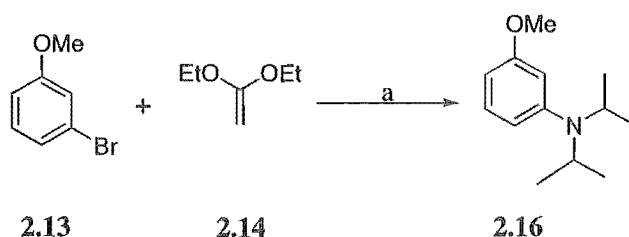
Jung and Lowen generated the benzyne by reacting *m*-bromoanisole **2.13** with LDA as outlined in method 2, and trapped it with furan to give the adduct **2.15** (Figure 2.8).^{50c}



Reagents and conditions: (a) LDA, THF, $-78\text{ }^{\circ}\text{C}$ to r.t., no yield quoted.

Figure 2.8 Jung and Lowen's benzyne generation.

No yield was quoted and few experimental details were disclosed regarding this procedure. Nonetheless, an attempt was made to trap the benzyne generated by this method, with 1,1-diethoxyethylene. Unfortunately, the only observed product was amine **2.16**, which results from nucleophilic addition of diisopropylamine to the benzyne (Figure 2.9).⁵² In order to get an idea of the efficiency of the reported reaction it was decided to repeat the original procedure. Generation of the benzyne in the presence of equimolar amounts of furan gave predominantly the amine and only a trace of the furan-derived adduct. It is possible a vast excess of the trapping agent is required in order to suppress the competitive nucleophilic addition of diisopropylamine to the benzyne and as this would not be appropriate for our system, alternative methods were investigated.

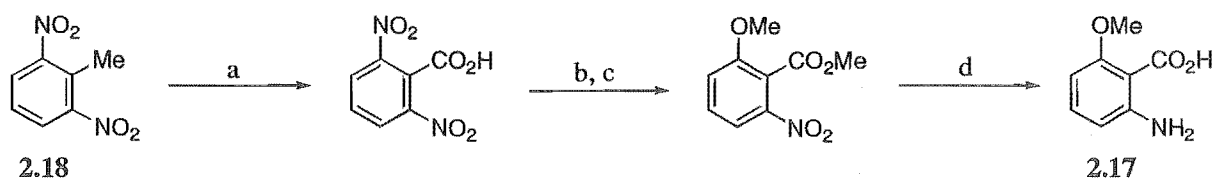


Reagents and conditions: (a) LDA, THF, -78°C to r.t.

Figure 2.9 Attempted trapping of 3-methoxybenzyne with 1,1-diethoxyethylene.

Iwao showed that 3-methoxybenzyne could be generated by treatment of *m*-chloroanisole with *s*-BuLi.^{50d} Due to the limited availability of *s*-BuLi* experiments were carried out using *n*-BuLi/K-*t*-butoxide, which has been reported to be a suitable replacement for *s*-BuLi in most instances.⁵³ However, treatment of *m*-chloroanisole with *n*-BuLi/K-*t*-butoxide, in the presence of 1,1-diethoxyethylene 2.14, gave only recovered starting material.

Diazotisation of amines such as 2.17 is a reliable method for generation of benzyne and this type of approach has been used in the preparation of 3,6-dimethoxybenzocyclobutenones.⁵⁴ However, synthesis of the benzyne precursors is not trivial. For example, 6-methoxyanthranilic acid (2.17), a precursor to 3-methoxybenzyne, has been prepared in 27 % yield from 2,6-dinitrotoluene (2.18), as shown below (Scheme 2.1).⁵⁵ Such a low yielding sequence would be detrimental to the overall yield of our proposed naphthalene synthesis. Thus, our attention was turned to generation of benzyne *via* method 5.

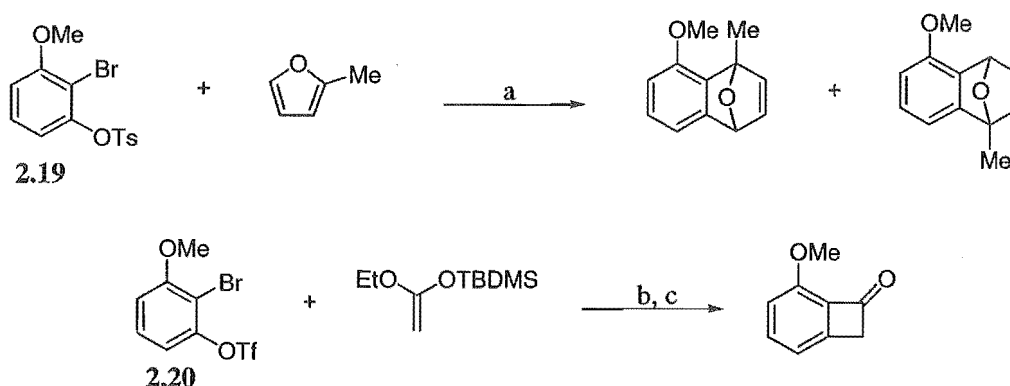


Scheme 2.1 Reagents and yields: (a) Conc. H_2SO_4 , $\text{Na}_2\text{Cr}_2\text{O}_7$, r.t., 58 %; (b) Me_2SO_4 , NaHCO_3 , acetone, reflux, 90 %; (c) NaOMe , MeOH , reflux, 73 %; (d) 10 % Pd/C, H_2 , MeOH , followed by $\text{NaOH}/\text{H}_2\text{O}$, reflux, 70 %.

It has been shown that 3-methoxybenzyne can be generated in an efficient manner by treatment of the bromosylate 2.19,^{50a} or iodotriplate 2.20,⁵⁶ with *n*-BuLi at low temperature.

* Due to the hazardous nature of this chemical even small quantities of this chemical must be shipped.

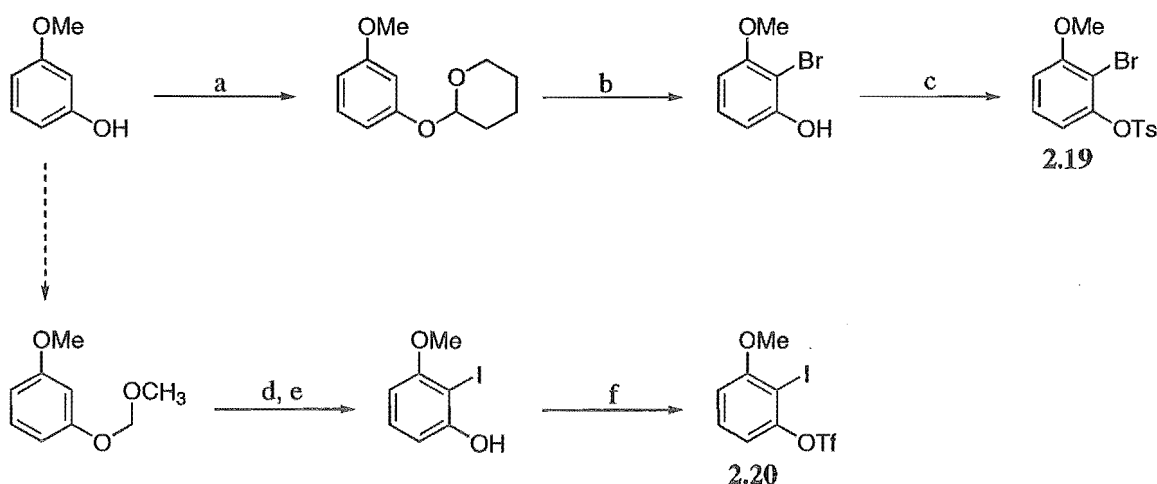
Halogen/metal exchange, followed by elimination of the leaving group, generates 3-methoxybenzyne, which can be efficiently trapped to give the desired adducts. Indeed, it has been shown that this approach is amenable to benzocyclobutenone synthesis as described in **Figure 2.10**.^{49b}



Reagents and yields: (a) *n*-BuLi, THF, $-100\text{ }^{\circ}\text{C}$ to r.t., 56 % 7:3; (b) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 89 %; (c) HF/H₂O, CH₃CN, $0\text{ }^{\circ}\text{C}$, 99 %.

Figure 2.10 Reactions of benzyne generated by halogen/metal exchange.

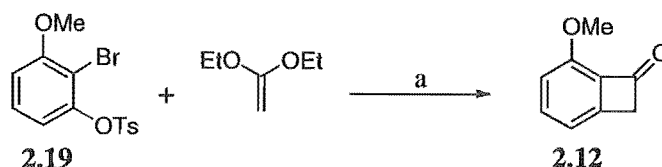
A drawback to this approach is the three step sequence required to synthesise each of the precursors **2.19**^{50a} and **2.20**⁵⁶. In addition, these sequences have moderate yielding steps that involve the generation and trapping of aryllithium species (**Figure 2.11**).



Reagents and yields: (a) DHP, cat TsOH, THF, $0\text{ }^{\circ}\text{C}$, 98 %; (b) *n*-BuLi, THF, r.t., BrCH₂CH₂Br, $0\text{ }^{\circ}\text{C}$; H₂O/HCl, 50 %; (c) TsCl, NEt₃, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$ to r.t., 92 %; (d) *t*-BuLi, TMEDA, Et₂O, I₂, $-78\text{ }^{\circ}\text{C}$; (e) TFA, CH₂Cl₂, r.t., 63 % for 2 steps; (f) Tf₂O, DMAP, pyridine, $0\text{ }^{\circ}\text{C}$, 100 %.

Figure 2.11 Synthesis of benzyne precursors.

Nonetheless, bromotosylate **2.19** was prepared according to the literature procedure.^{50a} Reaction of tosylate **2.19** with *n*-BuLi at $-95\text{ }^{\circ}\text{C}$, in the presence of 1,1-diethoxyethylene, proceeded smoothly and, after an acidic workup, benzocyclobutenone **2.12** was isolated in 78 % yield (Figure 2.12).

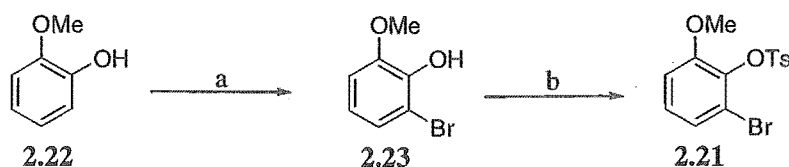


Reagents and yield: (a) *n*-BuLi, THF, $-95\text{ }^{\circ}\text{C}$ to r.t., then $\text{H}^+/\text{H}_2\text{O}$, 78 %.

Figure 2.12 Successful $[2\pi + 2\pi]$ cycloaddition.

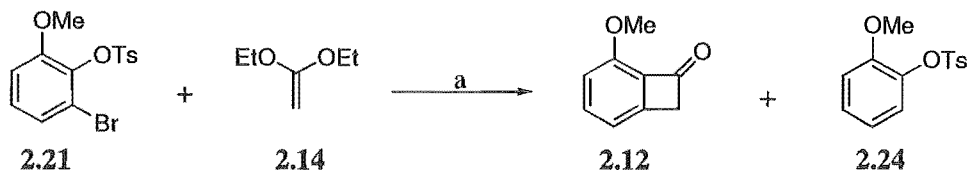
Although a pleasing result, the three-step sequence required for the synthesis of the benzyne precursor, coupled with the modest yield of the bromination step, was a drawback. In a projected naphthalene synthesis this would be detrimental to the overall efficiency of the process. Accordingly, we endeavoured to investigate an alternative benzyne precursor, the regioisomeric tosylate **2.21**.

Using a literature procedure, phenol **2.22** was selectively brominated using $\text{Br}_2/t\text{-BuNH}_2$ to give 2-bromo-6-methoxyphenol (**2.23**) in excellent yield.⁵⁷ Treatment of phenol **2.23** with triethylamine and tosyl chloride gave the tosylate **2.20** in quantitative yield. Thus, tosylate **2.21** could be generated in 90 % yield in just two steps from commercially available phenol **2.22** (Scheme 2.2).



Scheme 2.2 Reagents and yields: (a) Br_2 , *t*-BuNH₂, toluene, $-78\text{ }^{\circ}\text{C}$ to r.t., 91 %; (b) TsCl, NEt₃, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$ to r.t., 99 %.

However, reaction of tosylate **2.21** with *n*-BuLi in the presence of 1,1-diethoxyethylene **2.14** afforded only minor quantities of the desired adduct **2.12** upon acidic workup, with the main product isolated being debrominated material **2.24**⁵⁸ (Figure 2.13).



Reagents and yield: (a) *n*-BuLi, THF, -95°C to r.t., then $\text{H}^+/\text{H}_2\text{O}$, 22 % for **2.12**.

Figure 2.13 Reaction of alternative benzyne precursor **2.21** in the cycloaddition.

As no starting material was re-isolated, it would appear that halogen-metal exchange was not the problematic step. The lack of reactivity of the generated lithiospecies could be a result of insufficient leaving group ability or an intramolecular quenching as shown below (Figure 2.14).

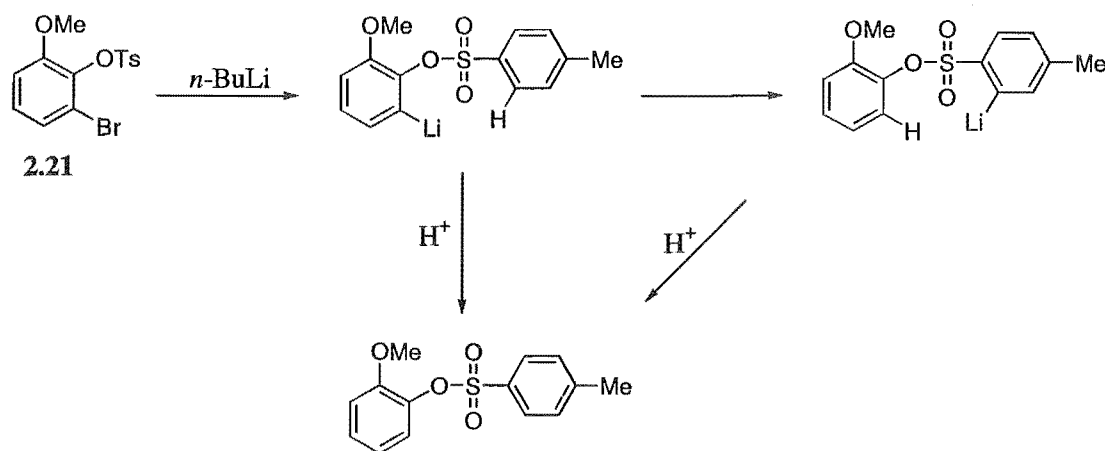
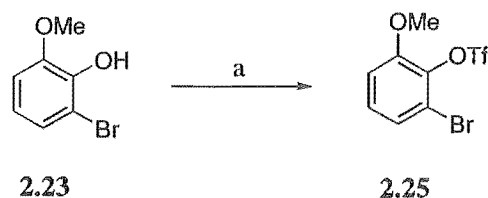


Figure 2.14 Possibilities for quenching of the lithiospecies.

This prompted investigation of the triflate leaving group as it has no sites for deprotonation and it is a better leaving group than a tosylate. The best method for preparation of triflate **2.25** was found to be reaction of phenol **2.23** with triflic anhydride in pyridine. Treatment with 1.1 equivalents of triflic anhydride gave triflate **2.25** in 78 % yield, which is slightly lower than expected for such a reaction.



Reagents and yield: (a) 1.1 eq Trf_2O , pyridine, 0 °C to r.t., 78 %.

Figure 2.15 Preparation of Triflate 2.25.

Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated the presence of another product. This product was found to be present in the distillation residue and purification of this by column chromatography gave a compound that could be crystallised from petroleum ether. The ^1H NMR spectrum was relatively similar to that of the phenol, showing a methoxy signal at 3.90 ppm and three aromatic signals whose coupling was indicative of a 1,2,3-trisubstituted aromatic (**Figure 2.16**).

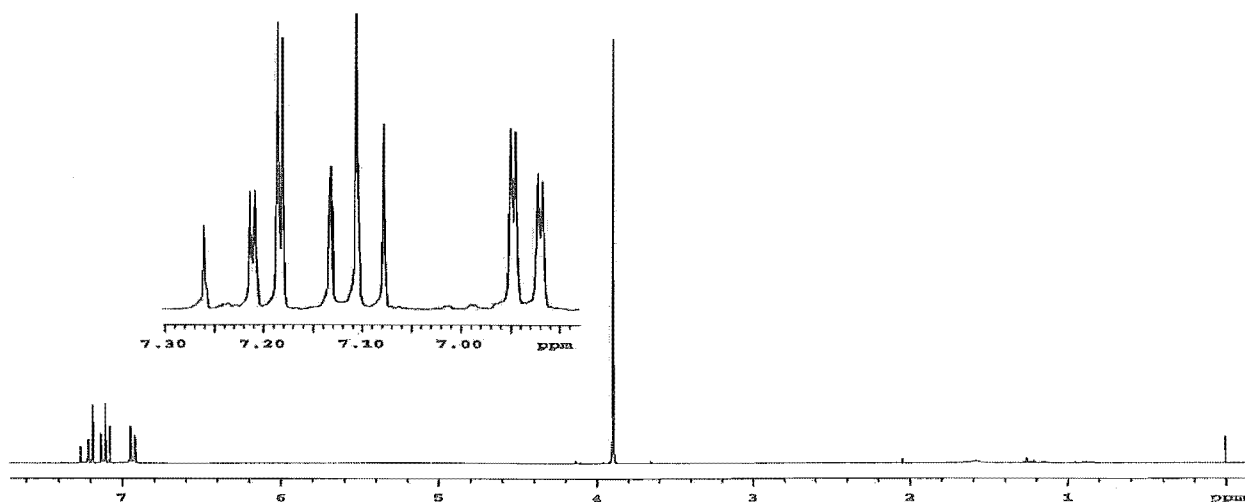


Figure 2.16 300 MHz ^1H NMR spectrum of the unknown.

The ^{13}C NMR spectrum showed 8 peaks, this included 6 aromatic carbons, a methoxy group, and an additional peak at 149 ppm. Examination of the infrared spectra revealed a peak at 1786 cm^{-1} , which is in the region for a $\text{C}=\text{O}$ stretch. Mass spectroscopy indicated a molecular formula of $\text{C}_{15}\text{H}_{12}\text{Br}_2\text{O}_5$, which suggested some sort of dimer. Fortunately, crystals of sufficient quality for X-ray analysis were obtained and this revealed that the product was carbonate 2.26. Formation

of this impurity was traced to the presence of the trifluoromethyl ester **2.27** in the triflic anhydride, which had been prepared by distillation of triflic acid from phosphorous pentoxide.⁵⁹ The ester **2.27** could be produced as a result of formation of small amounts of CF_3^+ in the reaction, which would immediately react with triflic acid.⁶⁰ Exposure of ester **2.27** to pyridine can produce difluorophosgene **2.28**. Accordingly, reaction of phenol **2.23** with phosgene **2.28** could then give rise to carbonate **2.26**, as detailed below (Figure 2.17).

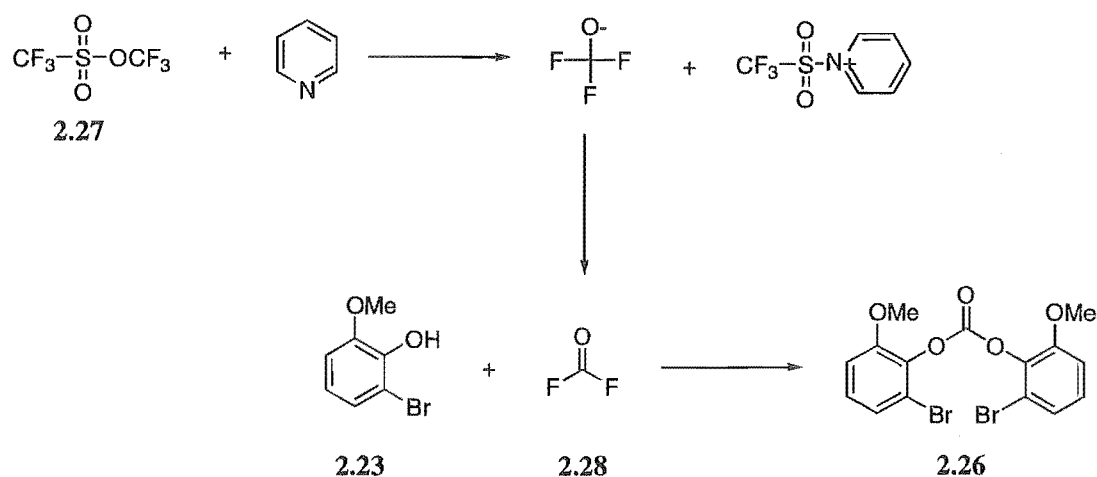
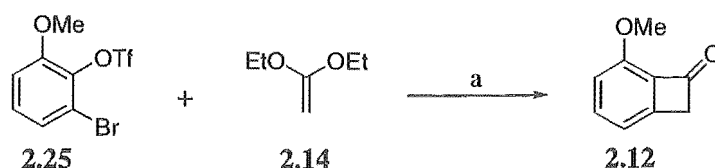


Figure 2.17 Proposed mechanism for the formation of carbonate **2.26**.

It was subsequently found that treatment of phenol **2.23** with 1.5 equivalents of triflic anhydride eliminated the formation of carbonate **2.26** and gave triflate **2.25** in 98 % yield.

Having optimised the formation of triflate **2.25**, its reaction with *n*-BuLi in the presence of 1,1-diethoxyethylene **2.14** was explored. In contrast to tosylate **2.21**, reaction of triflate **2.25** with *n*-BuLi in the presence of 1,1-diethoxyethylene **2.14** at $-95\text{ }^{\circ}\text{C}$ proceeded smoothly. Following acidic workup, benzocyclobutenone **2.12** was isolated in 72 % yield (Figure 2.18). Subsequent scaling up of the reaction, using 20 g of bromotriflate, allowed access to significant quantities of the benzocyclobutenone.



Reagents and yield: (a) *n*-BuLi, THF, $-95\text{ }^{\circ}\text{C}$ to r.t., then $\text{H}^+/\text{H}_2\text{O}$, 72 %.

Figure 2.18 Successful cycloaddition using alternative benzyne precursor **2.25**.

This was a pleasing result as benzocyclobutenone **2.12** was now readily available in large quantities in only 3 steps from commercially available material in 64 % overall yield. This was crucial in terms of the projected naphthalene synthesis, with regard to our aim of an efficient large-scale syntheses of such compounds.

2.2.2 Synthesis of Other Substituted Benzocyclobutenones

In the total synthesis of naphthylisoquinoline alkaloids, the choice of protecting group on the naphthalene moiety is critical. Isopropyl and methoxymethyl (MOM), protecting groups have proven to be optimal. Accordingly, the preparation of benzocyclobutenones **2.29** and **2.30** (where $\text{P} = i\text{-Pr}$ or MOM) would allow further flexibility in our proposed naphthalene synthesis.

The precursors to 6-alkoxybenzocyclobutenones **2.29** and **2.30** are the monoprotected catechols **2.31** and **2.32** (Figure 2.19).

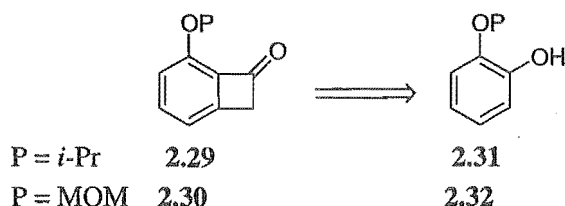
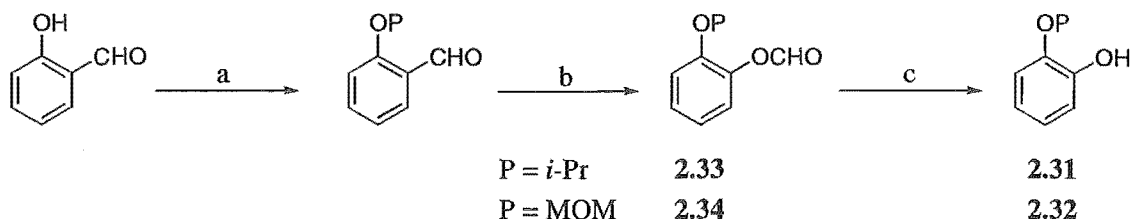


Figure 2.19 Precursors to 6-alkoxybenzocyclobutenones.

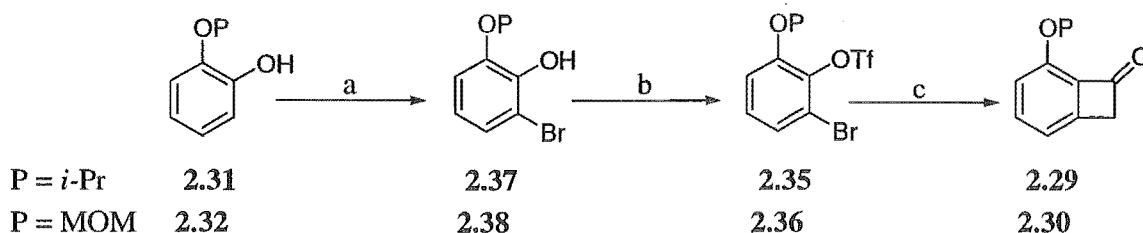
Although **2.31** is commercially available, phenols **2.31** and **2.32** were readily prepared according to the method described by Syper.⁶¹ Salicylaldehyde was protected with the appropriate

diphenyldiselenide and basic hydrogen peroxide, gave formate esters **2.33** and **2.34**. Cleavage of the esters with methanolic KOH gave the monoprotected catechols **2.31** and **2.32** in 88 % and 73 % yields respectively, for the three steps (Scheme 2.3).



Scheme 2.3 Reagents and yields: (a) MOM-Cl, Hünig's base, CH_2Cl_2 , r.t.; or $i\text{-PrBr}$, K_2CO_3 , DMF, r.t.; (b) $\text{H}_2\text{O}/\text{H}_2\text{O}_2$, $(\text{PhSe})_2$, CH_2Cl_2 , r.t.; (c) KOH, MeOH, r.t., $\text{P} = i\text{-Pr}$, 88 %, $\text{P} = \text{MOM}$ 73 % for 3 steps.

Preparation of the bromotriflates **2.35** and **2.36** is detailed in Scheme 2.4. *ortho*-Bromination using $\text{Br}_2/t\text{-BuNH}_2$ gave bromides **2.37** and **2.38** in 85 % and 80 % yields respectively. Reaction of the resulting bromides with triflic anhydride in pyridine gave the benzyne precursors **2.35** and **2.36** in excellent overall yield. Generation of the 3-alkoxybenzynes in the presence of 1,1-diethoxyethylene resulted in the expected $[2\pi + 2\pi]$ cycloaddition and, after an acidic workup, the benzocyclobutenones **2.29** and **2.30** were isolated in 62 % and 55 % yields respectively.



Scheme 2.4 Reagents and yields: (a) Br_2 , $t\text{-BuNH}_2$, toluene, -78°C to r.t., 85 % **2.37**, 80 % **2.38**; (b) Trf_2O , pyridine, 0°C to r.t.; 88 % **2.35**, 89 % **2.36**; (c) $n\text{-BuLi}$, 1,1-diethoxyethylene, THF, -95°C to r.t., then $\text{H}^+/\text{H}_2\text{O}$, 62 % **2.29**, 55 % **2.30**.

In summary, a two-step synthesis of precursors to 3-alkoxybenzynes has been developed, starting from readily available compounds. This has lead to an efficient, large scale synthesis of 6-alkoxybenzocyclobutenones.

2.3 Functionalisation of 6-Alkoxybenzocyclobutenones

With sufficient quantities of the benzocyclobutenones **2.12**, **2.29**, and **2.30** now in hand, functionalisation of these intermediates to provide useful naphthalene building blocks was investigated.

2.3.1 Bromination of 6-Alkoxybenzocyclobutenones

It was envisaged that the benzocyclobutenone derivatives could be selectively brominated in the *para*-position. This, after elaboration of the remaining portion of the naphthalene moiety, would give access to the desired functionalised naphthalenes such as **2.39**, as used in total syntheses of the naphthylisoquinoline alkaloids. (Figure 2.20).

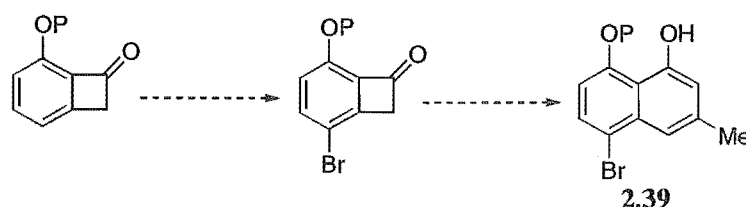
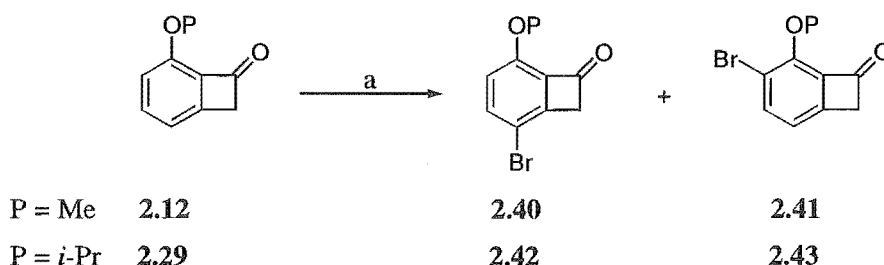


Figure 2.20 Projected naphthalene synthesis.

Initial studies on the bromination of benzocyclobutenone **2.12** with Br_2/CCl_4 , or *N*-bromosuccinimide/DMF, gave mixtures of *ortho*-bromo-, *para*-bromo-, and dibromobenzocyclobutenones, along with recovered starting material. As these were inseparable by chromatography, a more selective method of bromination was sought. Our attention was turned to benzyltrimethylammonium tribromide (BTMABr_3). It has been reported that this reagent is an excellent brominating agent for a variety of aromatic methyl ethers.⁶² Although commercially available this reagent can be readily prepared from benzyltrimethylammonium bromide.⁶³ Bromination of benzocyclobutenone **2.12** using BTMABr_3 in dichloromethane/methanol resulted in a very slow reaction, with starting material still predominant after 20 hours at room temperature. Even after four days at reflux there was still starting material present, so alternative conditions were explored. It has been reported that BTMABr_3 can be used to brominate less

reactive (electron poor), aromatic methyl ethers if the reaction is carried out in the presence of zinc chloride with acetic acid as the solvent.⁶² Bromination of benzocyclobutenone **2.12** under these conditions, as depicted in Figure 2.21, resulted in complete consumption of starting material within 24 hours. Examination of the crude material by ¹H NMR spectroscopy indicated the generation of a mixture of *ortho* and *para* isomers in a ratio of 88:12, in favour of the desired *para*-isomer. Purification by column chromatography gave the desired benzocyclobutenone **2.40** in 82 % yield, along with the *ortho*-bromo compound **2.41** in 9 % yield. This procedure was also used to successfully brominate benzocyclobutenone **2.29**, giving the desired product **2.42** in 80 % yield, along with 12 % of its regioisomer **2.43**.



Reagents and yields: (a) BTMABr₃, ZnCl₂, HOAc, r.t., **2.40** 82 %, **2.41** 9 %, **2.42** 80 %, **2.43** 12 %.

Figure 2.21 Bromination of benzocyclobutenones **2.12** and **2.29**.

2.3.2 Synthesis and Cyclisation of Acetylenic Benzocyclobutenols

Having found the appropriate conditions for selective bromination of the benzocyclobutenones, it was now possible to explore synthetic elaboration of the rest of the naphthalene moiety. Initially, a simple system was studied in order to assess the validity of the addition/cyclisation sequence to produce 1,8-dioxygenated naphthalenes. We chose the simple naphthol **2.44**⁶⁴, which is a key intermediate in the synthesis of the spirobisnaphthalene palmarumycin CP₁ (Figure 2.22).⁶⁵

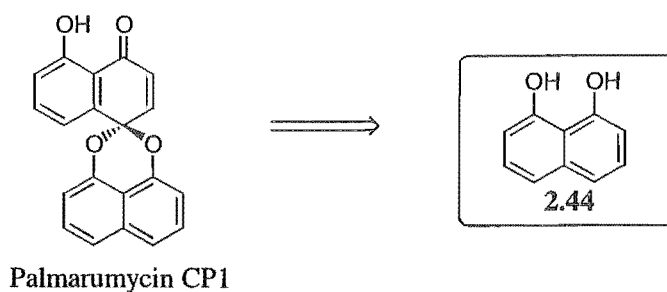
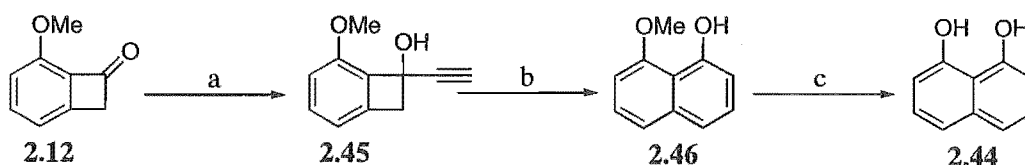


Figure 2.22 1,8-Dihydroxynaphthalene **2.44**, a key intermediate for the synthesis of palmarumycin CP₁.

Treatment of benzocyclobutenone **2.12** with 1.1 equivalents of ethynylmagnesium bromide in THF gave a mixture of starting material and the benzocyclobutenol **2.45** (Scheme 2.5). Reaction with 2 equivalents of the Grignard reagent resulted in consumption of starting material, but only 13 % conversion to the desired product. Changing the solvent to toluene, a less polar solvent, resulted in a much cleaner reaction of the benzocyclobutenone with ethynylmagnesium bromide. Purification by column chromatography gave the benzocyclobutenol **2.45** in 67 % yield.



Scheme 2.5 Reagents and yields: (a) ethynylmagnesium bromide, toluene, 0 °C, 67 %; (b) toluene, reflux, 60 %. (c) BBr₃, CH₂Cl₂, – 78 °C to r.t., 78 %.

Pleasingly the electrocyclic ring closure proceeded smoothly to give naphthol **2.46** in 60 % yield, after chromatography. Deprotection of naphthol **2.46** with BBr₃ in dichloromethane gave the desired naphthalendiol **2.44** in 78 % yield, after chromatographic purification.

With this result in hand, extension of this methodology to the synthesis of other substituted naphthalenes was investigated. As the naphthalene portion of naphthylisoquinoline alkaloids contains a methyl group at the 3-position, a different acetylene is required. This calls for a methyl group at the terminus of the acetylene, henceforth the addition and cyclisation of propynes was investigated.

Our initial focus was the synthesis of naphthalene **1.32**, as it is a valuable building block for the preparation of the naphthylisoquinoline alkaloids korupensamine C and ancistrobrevine B (Figure 2.23).³⁹

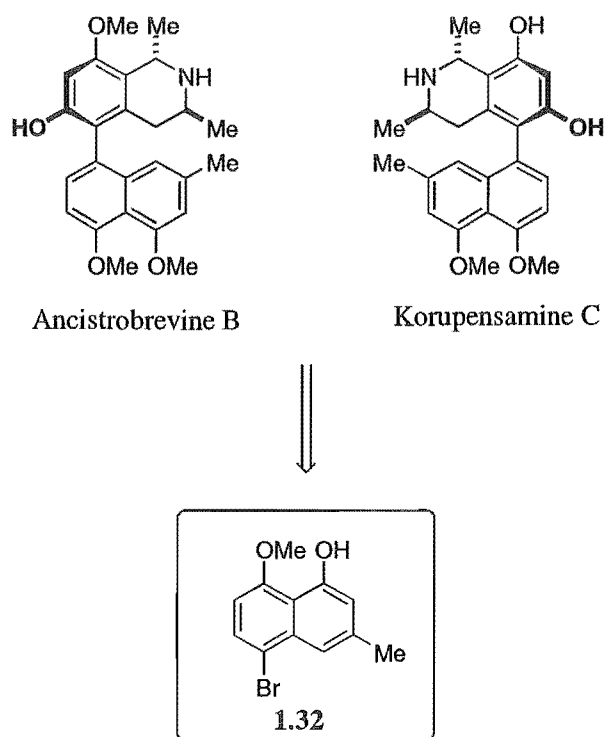
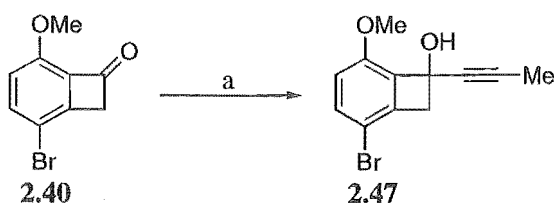


Figure 2.23 Naphthalene **1.32**, a naphthylisoquinoline alkaloid building block.

Addition of propynylmagnesium bromide to ketone **2.40**, using similar conditions to those successfully applied previously, resulted in isolation of the pure product **2.47** in only 30 % yield. Previous work on addition of various nucleophiles to benzocyclobutenones has shown that organolithium reagents are more reactive than Grignard reagents.⁴⁶ This allows these reactions to be conducted at much lower temperatures and reduces the possibility of undesirable reactions, such as ring opening of the intermediate alkoxy species. Propynyllithium has been generated by two methods: i) treatment of a solution of propyne with *n*-BuLi,⁶⁶ and ii) treatment of 1,2-dibromopropane with 3 equivalents of lithium diisopropylamide.⁶⁷ Generation of propynyllithium by the more convenient latter method involves a double elimination followed by lithiation of the terminal alkyne. Addition of ketone **2.40**, to the resulting solution of propynyllithium at $-60\text{ }^{\circ}\text{C}$, gave the desired benzocyclobutenol **2.47** in 72 % yield after purification by column chromatography (Figure 2.24).



Reagents and yields: (a) 1,2-Dibromopropane, LDA, THF, -60°C , 72 %.

Figure 2.24 Addition of propynyllithium to benzocyclobutenone **2.40**.

Unfortunately, thermolysis of the resulting adduct in toluene at reflux gave a mixture of products. Column chromatography on silica, using 30 % ethyl acetate/petroleum ether as the eluent, gave two fractions, the first of which contained a compound whose ^1H NMR spectrum is shown below (**Figure 2.25**).

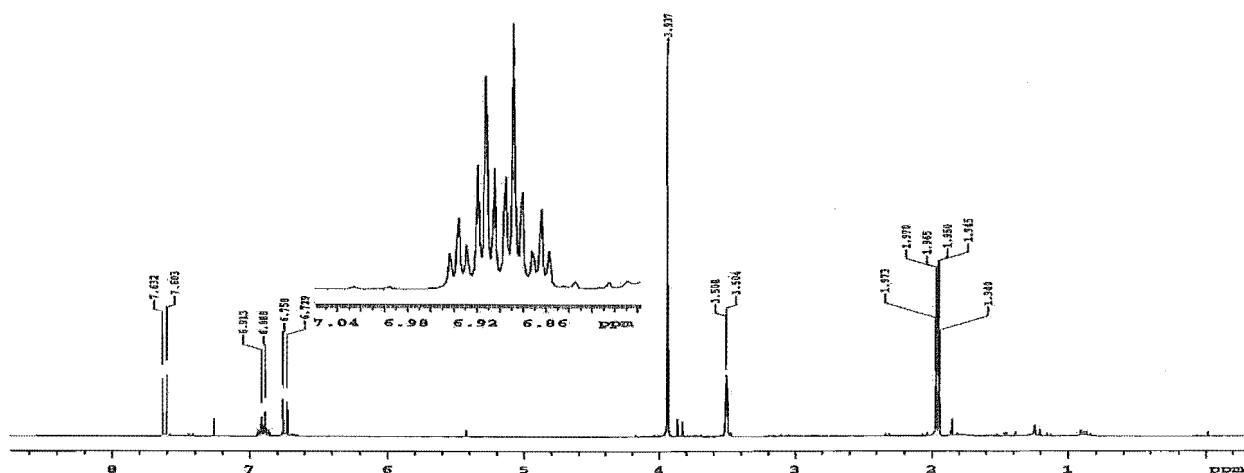


Figure 2.25 300 MHz ^1H NMR spectrum of the unknown.

The aromatic and methoxy signals were consistent with the aromatic core of the starting material, but the multiplet at 6.9 ppm was in the region expected for an olefinic proton. Irradiation of the signal at 3.5 ppm, in the ^1H NMR, caused the multiplet at 6.9 ppm to collapse to a quartet, and the CH_3 signal at 1.95 ppm to become a doublet (**Figure 2.26**).

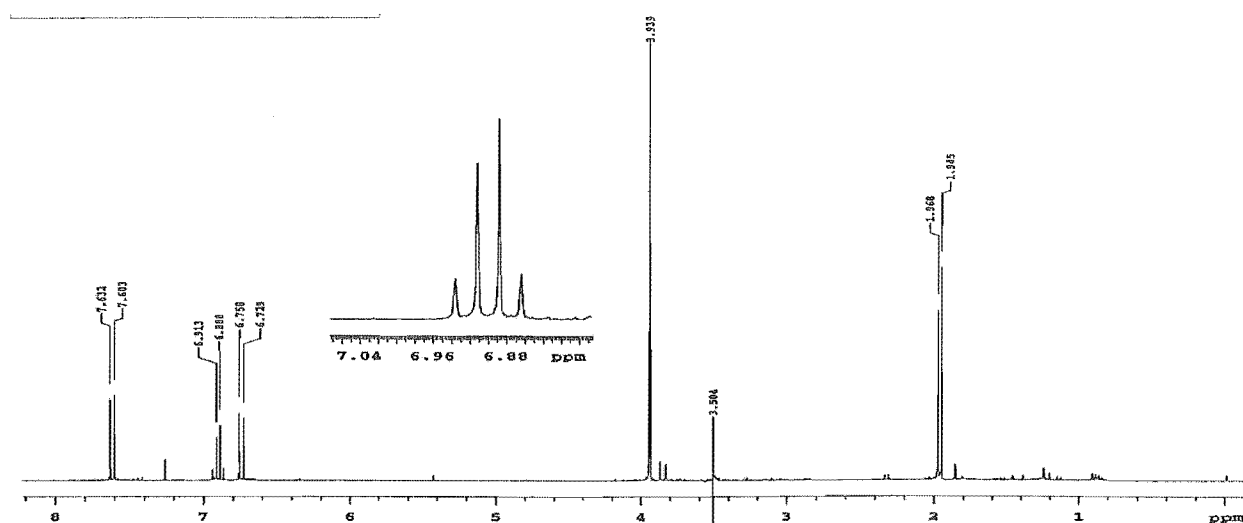
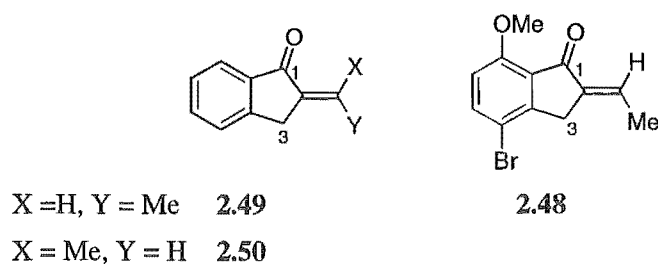


Figure 2.26 Selective irradiation of the multiplet at δ 1.96 ppm.

The infrared spectrum for this compound exhibited a signal at 1705 cm^{-1} , indicating the presence of a carbonyl group. Mass spectroscopy indicated a molecular formula of $\text{C}_{12}\text{H}_{11}\text{BrO}_2$, which is identical to the starting material, indicating a product resulting from a rearrangement. These results were consistent with the indanone **2.48** shown below. In their studies on allylic spin-spin coupling, Newsoroff and Sternhell studied two similar compounds **2.49** and **2.50**.⁶⁸ Examination of the chemical shifts and coupling constants of their two compounds further supported the proposed structure and provided evidence for the stereochemistry shown for the double bond (Figure 2.27).

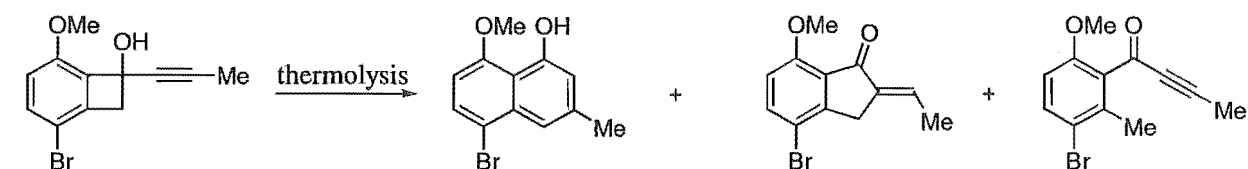


Compound	Coupling constants (Hz)	Chemical shifts (δ , ppm)
2.49 X = H, Y = Me	$J_{\text{X},3}$ 2.20, $J_{\text{Y},3}$ 1.18, $J_{\text{X},\text{Y}}$ 7.3	X 6.76, Y 1.92, H3 3.58
2.50 X = Me, Y = H	$J_{\text{Y},3}$ 1.67, $J_{\text{X},3}$ 1.57, $J_{\text{X},\text{Y}}$ 7.4	Y 6.24, X 2.28, H3 3.58
2.48	$J_{\text{CH},\text{CH}_2}$ 2.20, $J_{\text{CH}_3,\text{CH}_2}$ 1.47, $J_{\text{CH}_3,\text{CH}}$ 7.1	CH 6.90, CH_3 1.97, CH_2 3.51

Figure 2.27 Comparison of ^1H NMR data for related indanones.

The first fraction from the earlier column was found to contain the desired naphthalene **1.32**, along with what looked like a product resulting from ring opening of the cyclobutene moiety. This fraction was further purified by column chromatography, eluting with 20 % acetone/petroleum ether, to give naphthalene **1.32** in a disappointing 20 % yield, along with a small amount of the ring opened product **2.51**.

In an attempt to minimise the formation of indanone **2.48**, other solvents were investigated and the results shown below in **Figure 2.28**.



SOLVENT	1.32	2.48	2.51
toluene	49	50	trace
<i>m</i> -xylene	45	55	-
decalin	54	46	-
<i>n</i> -butanol	-	-	100
none	-	-	100

Figure 2.28 Product distribution after thermolysis in different solvents as determined by ^1H NMR analysis.

Unfortunately, little or no improvement on the yield of the desired naphthalene could be obtained. This prompted some thought on the origin of the five-membered ring product. The electrocyclic mechanism, which is assumed to operate in these types of systems, gives rise to the naphthalene framework as detailed below (**Figure 2.29**).⁴⁶

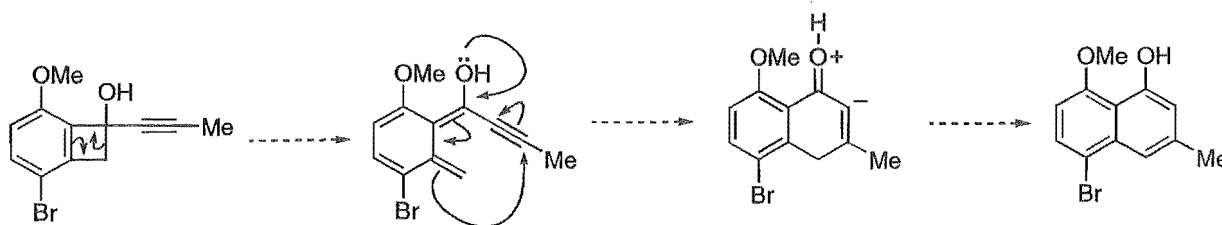


Figure 2.29 Possible electrocyclic mechanism.

However, a stepwise cyclisation can also be considered (Figure 2.30). This could account for the formation of the naphthalene (pathway A), and the indanone (pathway B), as well as for the exclusive formation of the ring opened product in the presence of a protic solvent (pathway C).

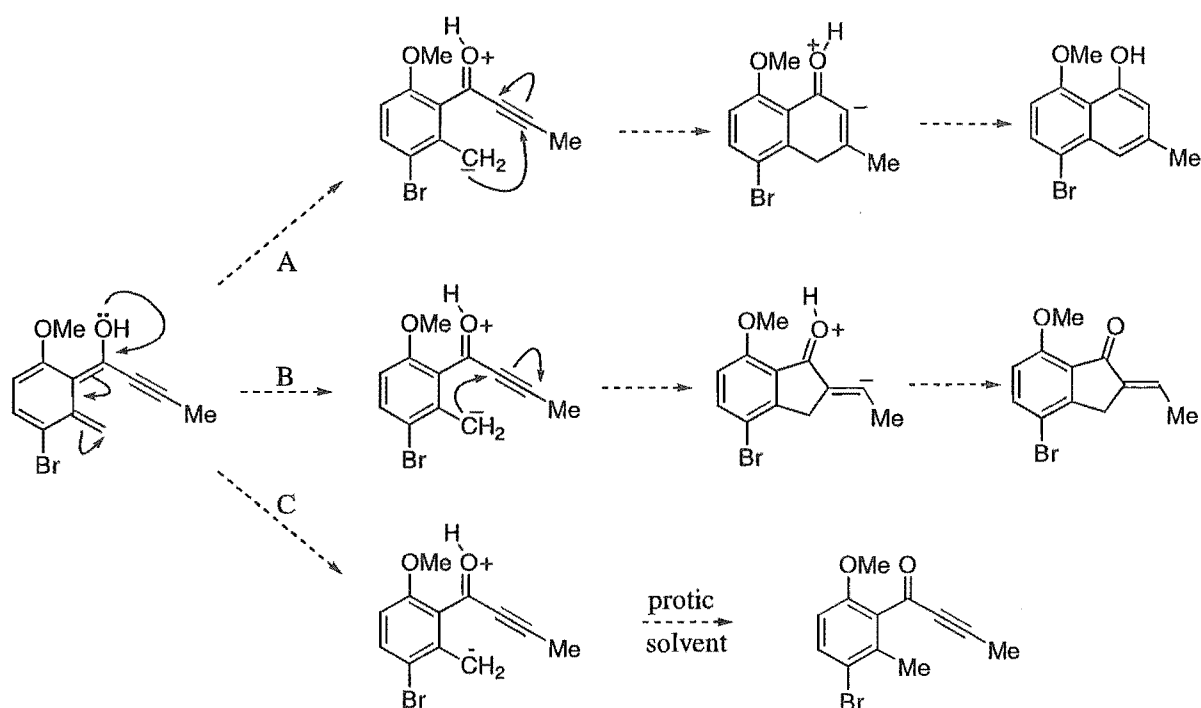


Figure 2.30 A possible non-concerted mechanism.

2.3.3 Synthesis and Cyclisation of Allenic Benzocyclobutenols

It was expected that the high electrophilicity of the central carbon atom of an allene group should ensure an efficient cyclisation, even if the reaction should proceed in a non-concerted fashion (Figure 2.31).

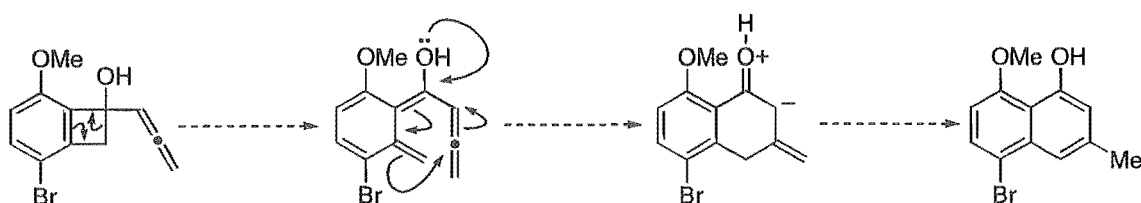
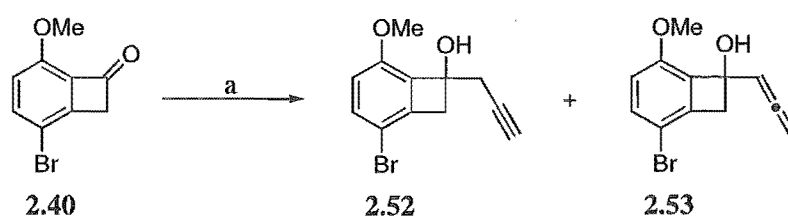


Figure 2.31 A proposed mechanism for cyclisation of an allenic alcohol.

Allenic alcohols have been prepared by addition of allenyllithium to ketones, although a mixture of allenic and acetylenic alcohols often results.⁶⁹ Nonetheless, this procedure warranted investigation. Bromoallene was prepared according to a literature procedure by isomerization of propargyl bromide.⁷⁰ Halogen/metal exchange gave allenyllithium,⁷¹ which upon reaction with ketone **2.40** gave predominantly the acetylenic product **2.52**, although a trace of the desired allenic alcohol **2.53** was present (Figure 2.32).



Reagents and yields: (a) *n*-BuLi, bromoallene, THF, -60 °C, 92 %, **2.52**:**2.53**, 95:5.

Figure 2.32 Addition of allenyllithium to benzocyclobutenone **2.40**.

Variation of reaction conditions gave no improvement on the product ratio. However, it was possible that the propargylic acetylene **2.52**, upon thermolysis, could cyclise in one of two ways. The first would lead to a seven-membered ring and the second, to the more favoured naphthalene (Figure 2.33).

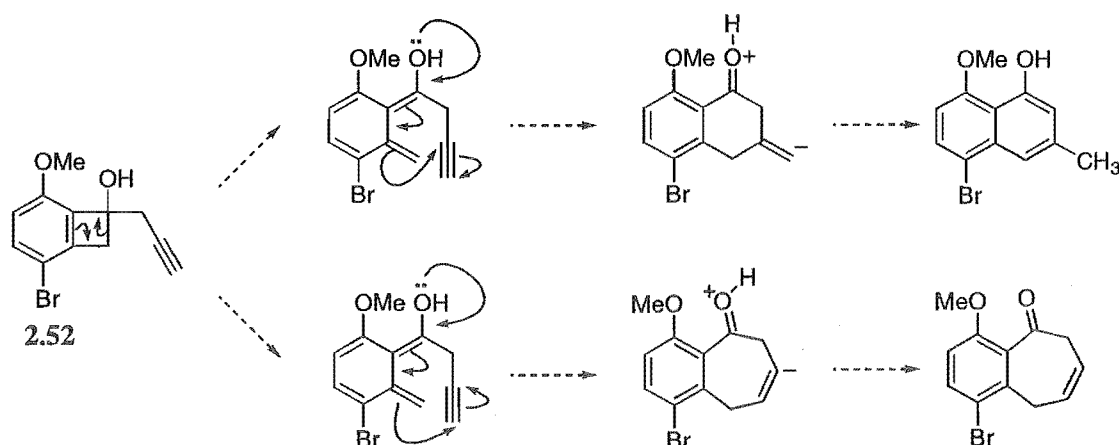
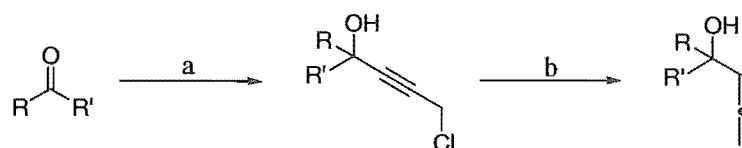


Figure 2.33 Possible cyclisation of propargylic benzocyclobutenone **2.52**.

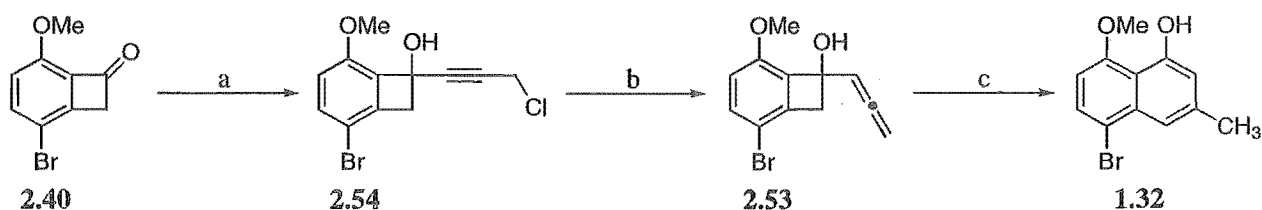
Thermolysis of the mixture of compounds was performed in refluxing toluene. Analysis of a sample by ^1H NMR spectroscopy after 2 hours reaction time revealed that the propargylic acetylene was unreacted, but no allenic alcohol was present and a comparative amount of naphthalene had formed. Continued thermolysis gave no further naphthalene indicating that only the trace amount of allenic alcohol was producing the desired naphthalene. This indicated that if allenic alcohol **2.53** could be prepared selectively, this process would constitute an efficient synthesis of 1,8-dioxygenated naphthalenes containing a methyl group in the 3-position.

An alternative procedure for the synthesis of allenic alcohols⁷² involves the hydroxyl-directed reduction of propargyl chlorides, which gives allenic alcohols exclusively (Scheme 2.6).⁷³



Scheme 2.6 Reagents and conditions: (a) Propargyl chloride, $n\text{-BuLi}$, THF; (b) LiAlH_4 , Et_2O .

Propargyl chloride was prepared according to a literature method⁷⁴ and lithiated at the terminal acetylenic position.⁷⁵ Reaction of the lithiospecies with ketone **2.40** gave acetylenic alcohol **2.54** in 95 % yield. Subsequent hydroxyl-directed reduction of acetylene **2.54** with lithium aluminium hydride in THF gave allenic alcohol **2.53** in a pleasing 95 % yield. Thermolysis of allenic alcohol **2.53** proceeded smoothly to afford naphthalene **1.32** in a gratifying 84 % yield, with no trace of the indanone side-product (Scheme 2.7). Thus, naphthalene **1.32** was readily generated in 3 steps in 76 % overall yield from readily available benzocyclobutenone **2.40**.



Scheme 2.7 Reagents and yields: (a) 3-Chloro-1-propynyllithium, THF, $-60\text{ }^\circ\text{C}$, 95 %; (b) LiAlH_4 , THF, $0\text{ }^\circ\text{C}$, 95 %; (c) toluene, reflux, 84 %.

With a method for the synthesis of 1,8-dioxygenated naphthalenes containing a methyl group at C3 of the naphthalene now in hand, investigation into the synthesis of other useful naphthalene building blocks was pursued. Naphthalene **2.55** is a required intermediate in the synthesis of the naphthylisoquinoline alkaloids korupensamine A and B (**Figure 2.34**).^{34a}

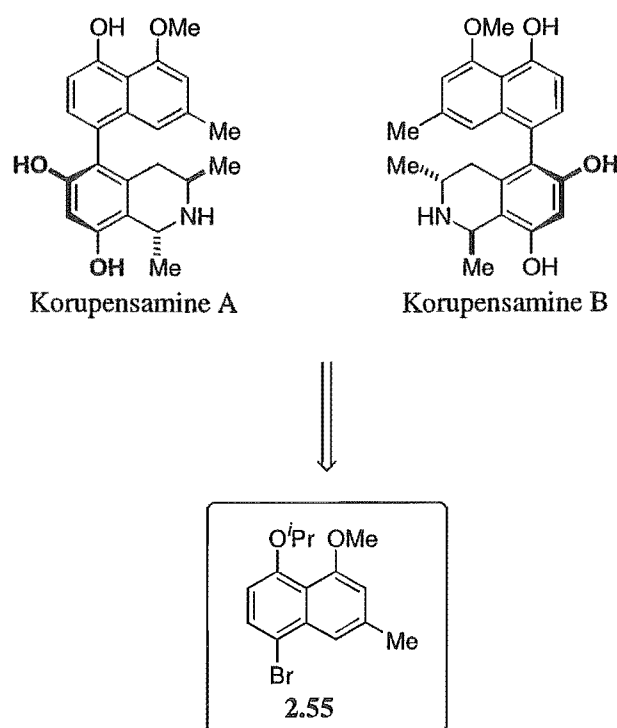
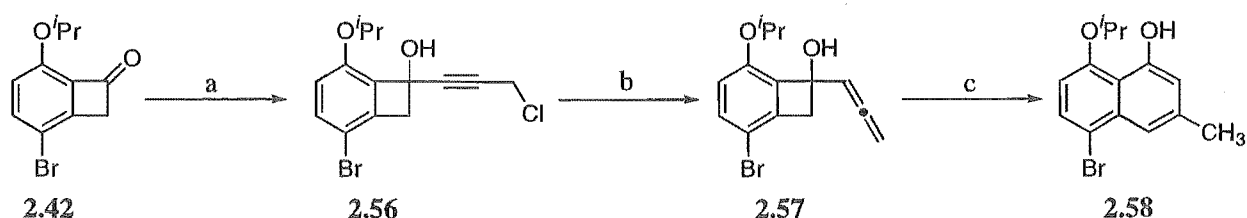


Figure 2.34 Naphthalene **2.55**, a precursor to korupensamines A and B.

Starting with benzocyclobutenone **2.42**, addition of lithiopropargylchloride gave acetylene **2.56**. Reduction of **2.56** with lithium aluminium hydride gave allene **2.57**, which was smoothly converted into naphthol **2.58** as described above (**Scheme 2.8**). *O*-Methylation of naphthalene **2.58** would generate the natural product precursor **2.55** shown above. This had been previously synthesised by a 10-step sequence starting from 3-hydroxybenzaldehyde.^{34a}



Scheme 2.8 Reagents and yields: (a) 3-Chloro-1-propynyllithium, THF, -60 °C, 84 %; (b) LiAlH₄, THF, 0 °C, 99 %; (c) toluene, reflux, 76 %.

To extend the versatility of this chemistry, the syntheses of naphthalenes **2.59** and **2.60** were investigated. Naphthalenes **2.59** and **2.60** have been used in the syntheses of the natural products sty pandrol⁷⁶ and dioncophylline C^{37d,e} respectively (Figure 2.35).

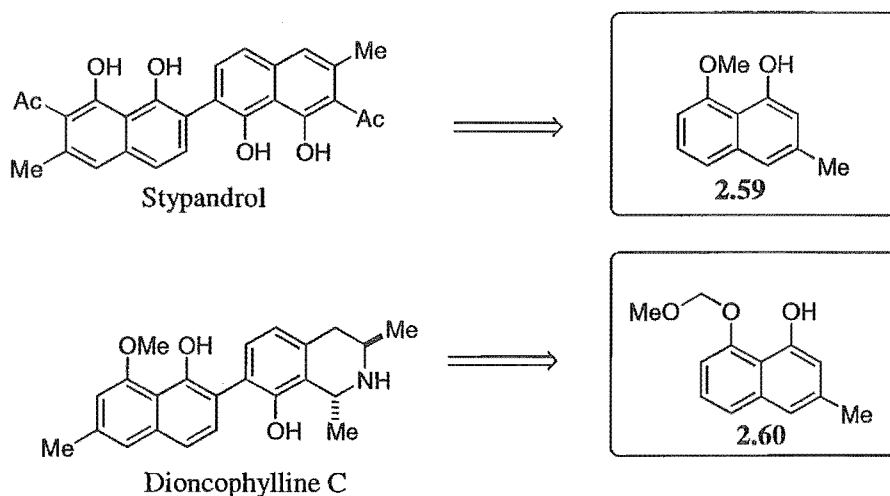
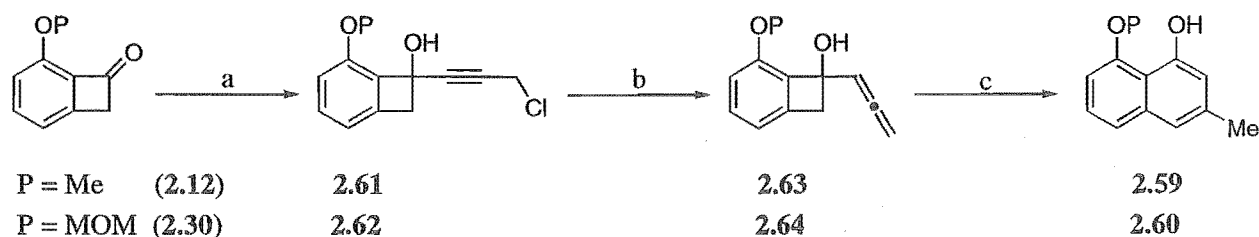


Figure 2.35 Other useful naphthalene building blocks.

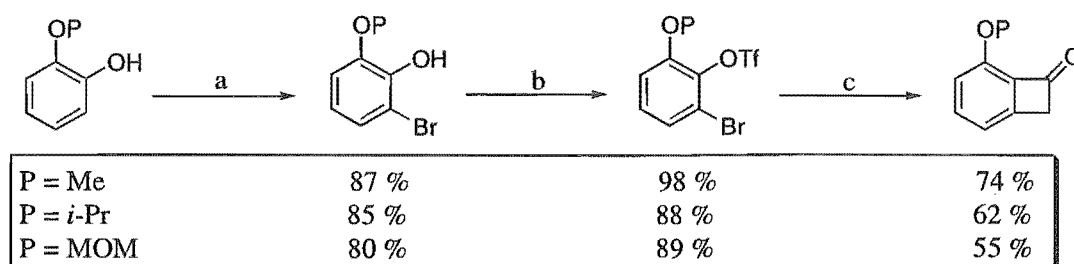
Addition of lithiopropargylchloride to benzocyclobutenones **2.12** and **2.30** proceeded smoothly, as did reduction of the resulting propargyl chlorides **2.61** and **2.62**. Pleasingly, thermolysis of allenic alcohols **2.63** and **2.64** gave the desired naphthols in good yields, which demonstrated that this synthetic sequence was applicable to a number of useful naphthalene building blocks (Scheme 2.9).



Scheme 2.9 Reagents and yields: (a) 3-Chloro-1-propynyllithium, THF, -60 °C, **2.61** 76 %, **2.62** 60 %; (b) LiAlH₄, THF, 0 °C, **2.63** 91 %, **2.64** 97 %; (c) toluene, reflux, **2.59** 80 %, **2.60** 79 %.

2.4 Summary

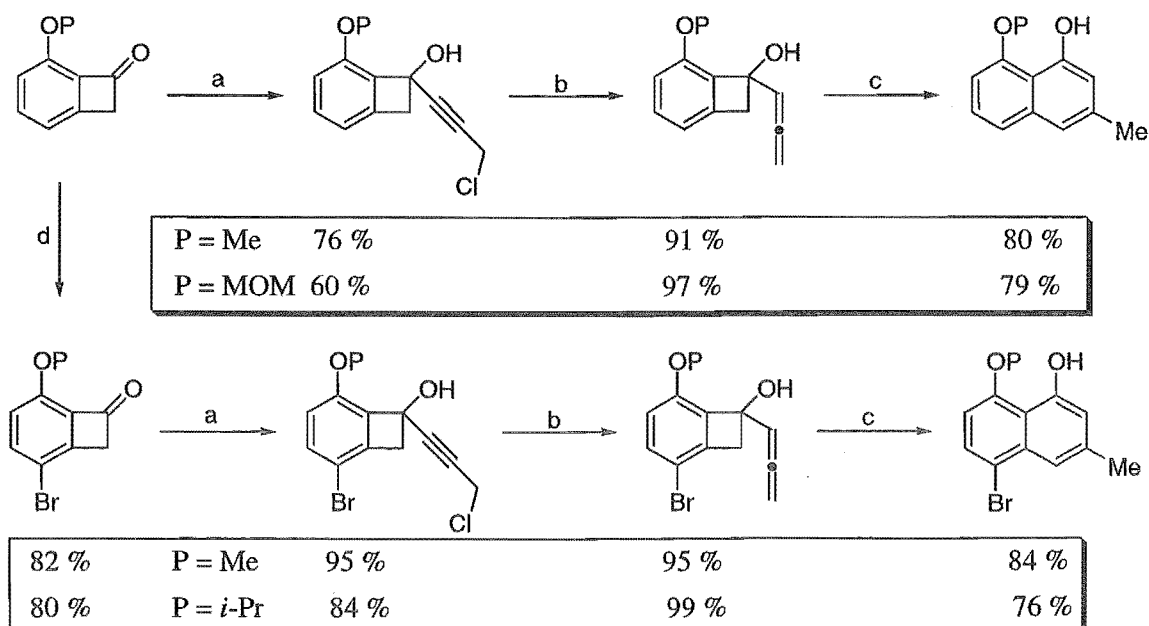
In summary, a short route to precursors for 3-alkoxybenzynes has been developed, starting from readily available compounds. This has allowed an efficient, large scale synthesis of 6-alkoxybenzocyclobutenones to be developed.⁷⁷ These compounds are useful synthetic intermediates, which can be readily functionalised. (Figure 2.36).



Reagents and conditions: (a) Br₂, *t*-BuNH₂, toluene, -78 °C to rt.; (b) Tf₂O, pyridine, 0 °C to rt.; (c) 1,1-diethoxyethylene 2.14, *n*-BuLi, THF, -95 °C to rt, then H⁺/H₂O.

Figure 2.36 Synthesis of 6-alkoxybenzocyclobutenones.

An alternative route for the synthesis of naphthalene building blocks was then developed, starting from the now readily available 6-alkoxybenzocyclobutenones (Figure 2.37).⁷⁸



Reagents and conditions: (a) 3-Chloro-1-propynyllithium, THF, -60 °C; (b) LiAlH₄, THF, 0 °C; (c) toluene, reflux. (d) BTMABr₃, ZnCl₂, HOAc, r.t.

Figure 2.37 Synthesis of functionalised 1,8-dioxygenated naphthalenes.

Significant advantages of this approach are the ability to readily scale up the sequence, its compatibility with various protecting groups, and the ability to vary functionality. The flexibility of this sequence of reactions should allow access to other substituted naphthalenes, provided the necessary benzocyclobutenone can be generated.

Chapter Three

Synthetic Approaches to
Ancistrocladidine Proceeding
via Benzocyclobutenols

3.1 An Approach based on an Allenylbenzocyclobutenol

3.1.1 Introduction

With the establishment of a method for the synthesis of naphthalene precursors from benzocyclobutenones, efforts were now focused on application of this type of chemistry to the synthesis of the 7-3' linked naphthylisoquinoline alkaloid ancistrocladidine **1.99** (Figure 3.1).

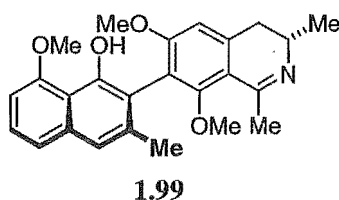


Figure 3.1 Ancistrocladidine.

It was shown in Chapter 2 that upon thermolysis 1-allenyl-6-alkoxybenzocyclobuten-1-ols readily cyclise to afford the corresponding 8-alkoxy-3-methyl-1-naphthols in good yields. Indeed the naphthalene portion of ancistrocladidine was efficiently synthesised by such a reaction (Figure 3.2).



Figure 3.2 Thermolysis of an allenic alcohol.

This efficient cyclisation protocol could be incorporated into a synthesis of ancistrocladidine if the 1,1-disubstituted allene **3.1** shown below could be prepared (Figure 3.3). Upon thermolysis, benzocyclobutenol **3.1** should give the correctly functionalised naphthalene.

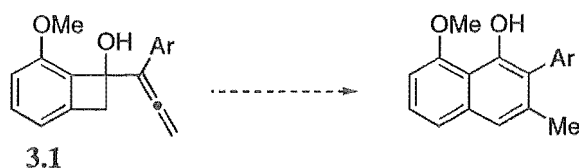


Figure 3.3 Thermolysis of a 1,1-disubstituted allene to give an *ortho*-aryl naphthol.

Two possible routes to allenic alcohol 3.1 can be considered (Figure 3.4). Firstly, a palladium-catalysed coupling between the propargyl chloride 3.2 and arylmetal species 3.3 could give the desired allenic alcohol. Secondly, a reaction of lithiospecies 3.4 with benzocyclobutenone 2.12 could give the desired intermediate.

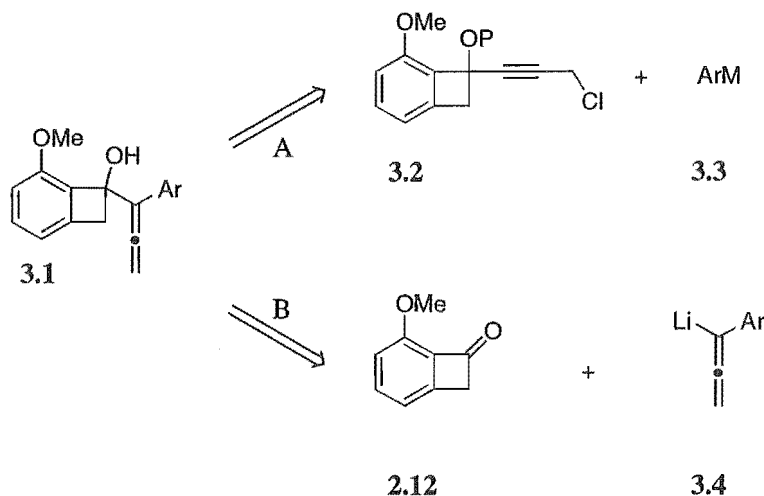


Figure 3.4 Retrosynthesis of allenic alcohol 3.46.

Compounds such as 3.1 could be generated containing the entire dihydroisoquinoline moiety; or containing a precursor to the dihydroisoquinoline moiety (Figure 3.5). Either of these approaches requires access to intermediates that have functionality between the methoxy groups such as 3.5 and 3.6.

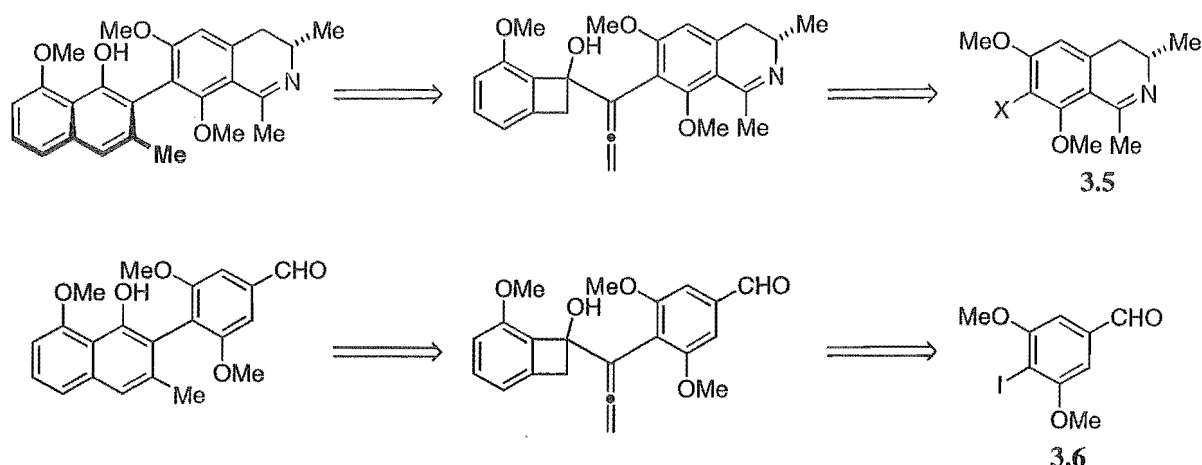


Figure 3.5 Possible precursors to ancistrocladidine.

3.1.1.1 Introduction of Functionality between the Methoxy Groups

As dihydroisoquinoline **1.5** is a known compound¹¹ direct manipulation of this intermediate could provide rapid access to a functionalised 3,4-dihydroisoquinoline. It was envisaged that this could be achieved by a directed *ortho*-metalation reaction.⁷⁹ The directed *ortho*-metalation reaction involves deprotonation of a site *ortho* to a heteroatom-containing group by a strong base, normally an alkyllithium reagent. Subsequent quenching of the resulting *ortho*-lithiated intermediate gives the desired *ortho*-substituted product (Figure 3.6).

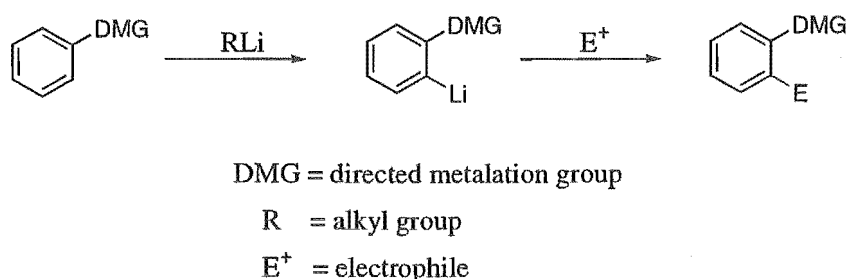


Figure 3.6 The directed *ortho*-metalation reaction.

The methoxy group has been shown to be an excellent director of *ortho*-metalation due to its ability to exhibit both inductive and coordinative effects. A co-operative effect of 1,3-interrelated directing groups also operates in the directed *ortho*-metalation reaction. Therefore,

directed metalation between the methoxy groups of the heterocyclic portion of the ancistrocladidine is one potential avenue of investigation (Figure 3.7).

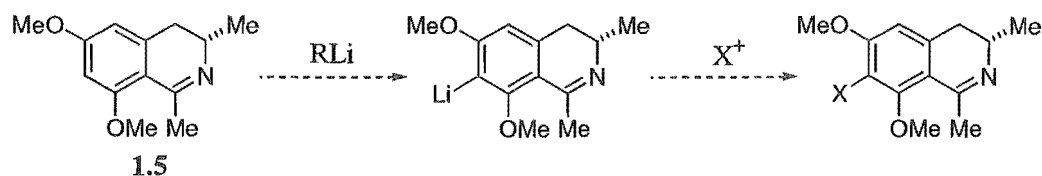


Figure 3.7 Possible functionalisation of dihydroisoquinoline **1.5** by directed *ortho*-metalation.

Alternatively, various halogenated derivatives of 3,5-dimethoxybenzaldehyde have been synthesised in 6 steps from 3,5-dihydroxybenzoic acid (Figure 3.8).⁸⁰ Following protection of the reactive aldehyde moiety, these intermediates could be manipulated to give an appropriately functionalised precursor to a 3,4-dihydroisoquinoline.

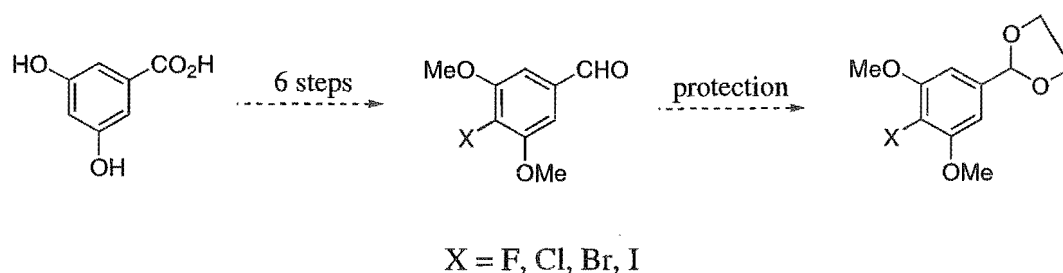


Figure 3.8 Synthesis of a functionalised dihydroisoquinoline precursor.

3.1.1.2 Manipulation of Functionality between the Methoxy Groups.

Disconnection A from Figure 3.4 requires a metalated aromatic moiety **3.3**. Such a compound could be obtained from the appropriate lithiospecies, derived from either the directed *ortho*-metalation of dihydroisoquinoline **1.5**, or from halogen/metal exchange of halide **3.7** (Figure 3.9).

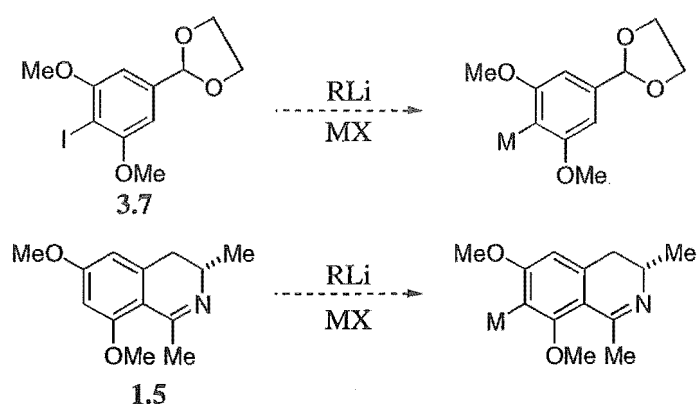


Figure 3.9 Possible intermediates for a palladium-catalysed coupling.

Disconnection B identifies allenyllithium species as key starting materials. As allenes are isomers of acetylenes, it was envisaged that the allenic precursors could be derived from an aryl acetylene. These aryl acetylenes could be prepared from aryl halides, 3.7 or 3.5, by the Sonogashira reaction (Figure 3.10).⁸¹

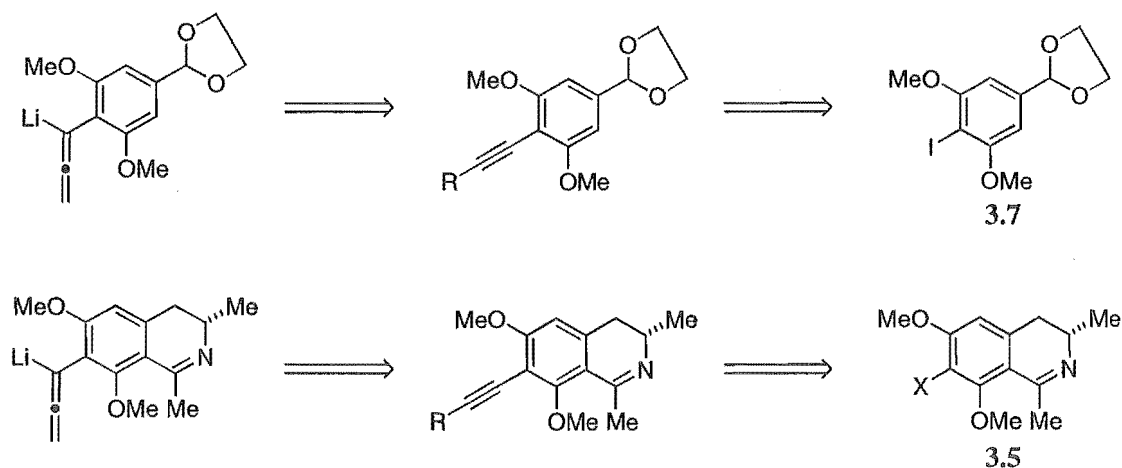


Figure 3.10 Disconnection of the allenyllithiums.

3.1.1.3 Summary

In summary, two approaches have been considered for formation of the biaryl-bond present in ancistrocladidine (**Figure 3.11**). Firstly, a palladium-catalysed coupling between arylmetal species **3.3** and propargyl chloride **3.2**, and secondly, addition of allenyllithium **3.4** species to benzocyclobutenone **2.12**. Within these two approaches either the entire dihydroisoquinoline moiety can be utilised, or a precursor to the dihydroisoquinoline can be used.

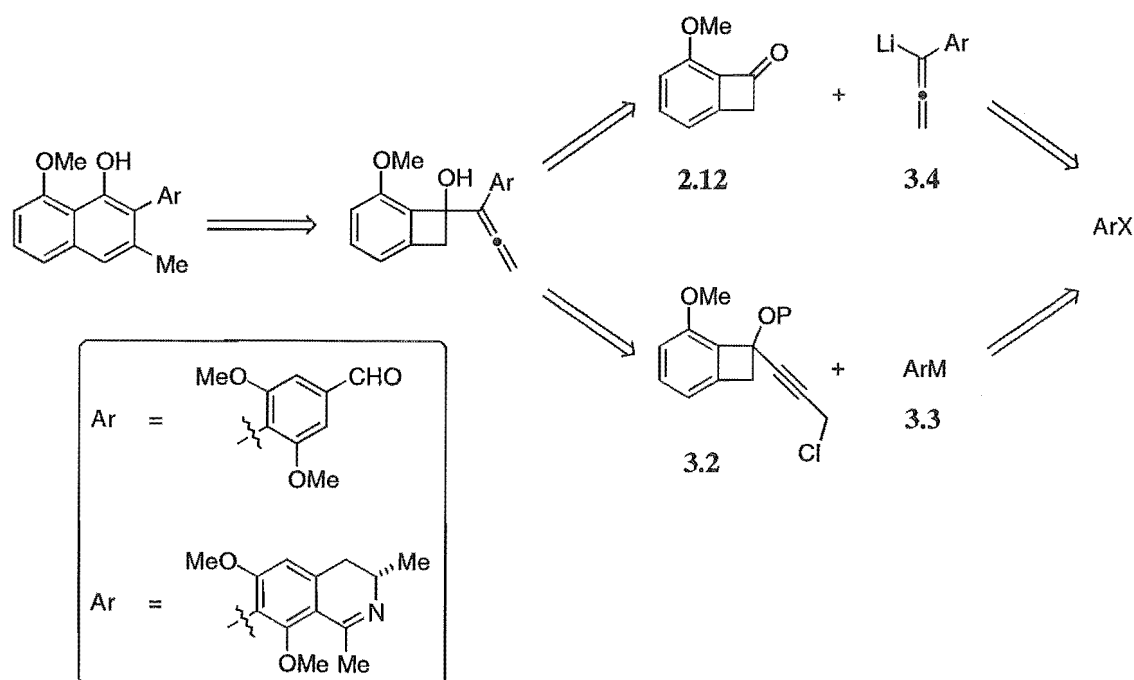


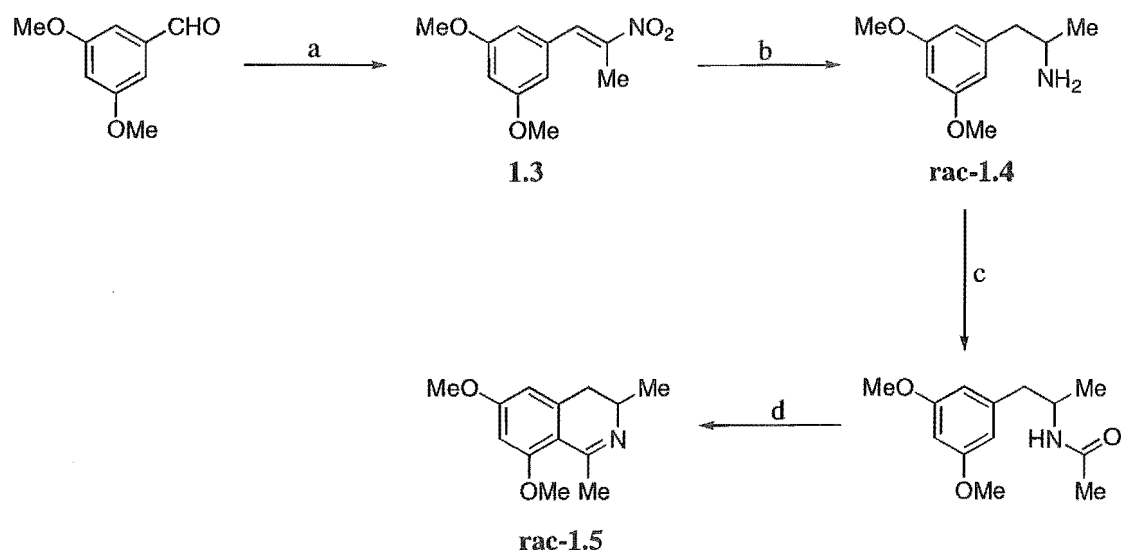
Figure 3.11 Summary of possible approaches involving allenic alcohols.

3.1.2 Attempted Functionalisation of the Heterocyclic Moiety

3.1.2.1 Synthesis of the Dihydroisoquinoline

For initial functionalisation studies on the heterocyclic moiety, racemic material was deemed adequate. Accordingly, racemic dihydroisoquinoline **rac-1.5** was synthesised from 3,5-dimethoxybenzaldehyde, using the method described by Sargent and Rizzacasa.¹¹ Refluxing the aldehyde with nitroethane and ammonium acetate in acetic acid gave the nitrostyrene **1.3** in 98 %

yield. The nitrostyrene was reduced with lithium aluminium hydride in THF at reflux to give racemic amine **1.4** in 91 % yield. The standard acetylation followed by Bischler-Napieralski cyclisation gave dihydroisoquinoline **rac-1.5** in 94 % yield over 2 steps (Scheme 3.1).



Scheme 3.1 Reagents and yields: (a) NH_4OAc , EtNO_2 , HOAc , reflux, 98 %; (b) LiAlH_4 , THF, reflux, 91 %; (c) AcCl , NEt_3 , CH_2Cl_2 , 0 °C; (d) POCl_3 , CH_3CN , reflux, 94 % for 2 steps.

3.1.2.2 Attempted *ortho*-Metalation of the Heterocyclic Moiety

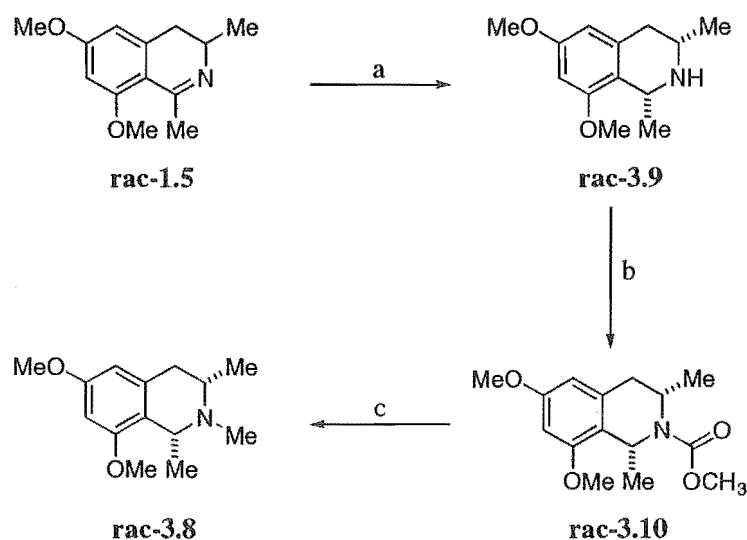
The initial metalation procedures used were those which have been successfully applied to the metalation of 1,3-dimethoxybenzene (Figure 3.12).^{82,83,84}

Reference	Metalation conditions	Electrophile	% Yield
82	$n\text{-BuLi}/\text{Et}_2\text{O}/-35$ to -78 °C	Me_2CHCOCl	78
83	$n\text{-BuLi}/\text{THF}/-5$ to 25 °C	$(\text{MeS})_2$	100
84	$n\text{-BuLi}/\text{Et}_2\text{O}/25$ °C	CuBr	93

Figure 3.12 Metalation of 1,3-dimethoxybenzene.

Unfortunately reaction of dihydroisoquinoline **rac-1.5** with $n\text{-BuLi}$ using the same range of conditions shown in Figure 3.12, followed by quenching the reaction with deuterated methanol, gave a complex mixture.

As the imine moiety is electrophilic and could be attacked by an alkyllithium reagent, the 3,4-dihydroisoquinoline was converted into tetrahydroisoquinoline **3.8** using the reported procedures (Scheme 3.2).^{29d} Reduction of dihydroisoquinoline **rac-1.5** with sodium borohydride in methanol gave the racemic *cis*-configured tetrahydroisoquinoline **3.9**. To avoid quaternary ammonium salt formation, *N*-methylation is carried out using a two-step procedure. This involves preparation of carbamate **rac-3.10** by reaction of amine **rac-3.9** with methyl chloroformate and sodium bicarbonate in dichloromethane, which can then be reduced with lithium aluminium hydride in tetrahydrofuran at reflux, to give *cis-N*-methyltetrahydroisoquinoline **3.8** in 90 % yield over 3 steps.



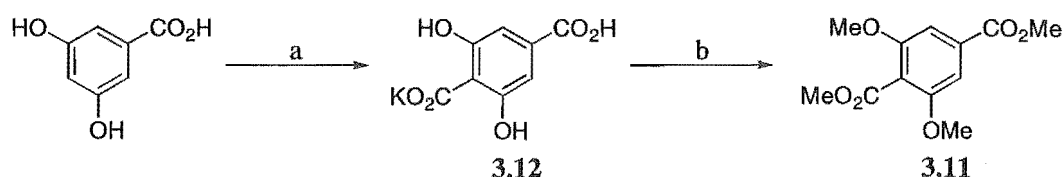
Scheme 3.2 Reagents and yield: (a) NaBH₄, MeOH, r.t.; (b) ClCO₂Me, NaHCO₃, CH₂Cl₂, r.t.; (c) LiAlH₄, THF, reflux, 90 % over 3 steps.

Despite numerous attempts, using a variety of conditions, the metalation between the methoxy groups of tetrahydroisoquinoline **rac-3.8** could not be achieved. The lack of success of this approach led to discontinuation and investigation of other functionalised precursors.

3.1.3 Introduction of Functionality at an Earlier Stage

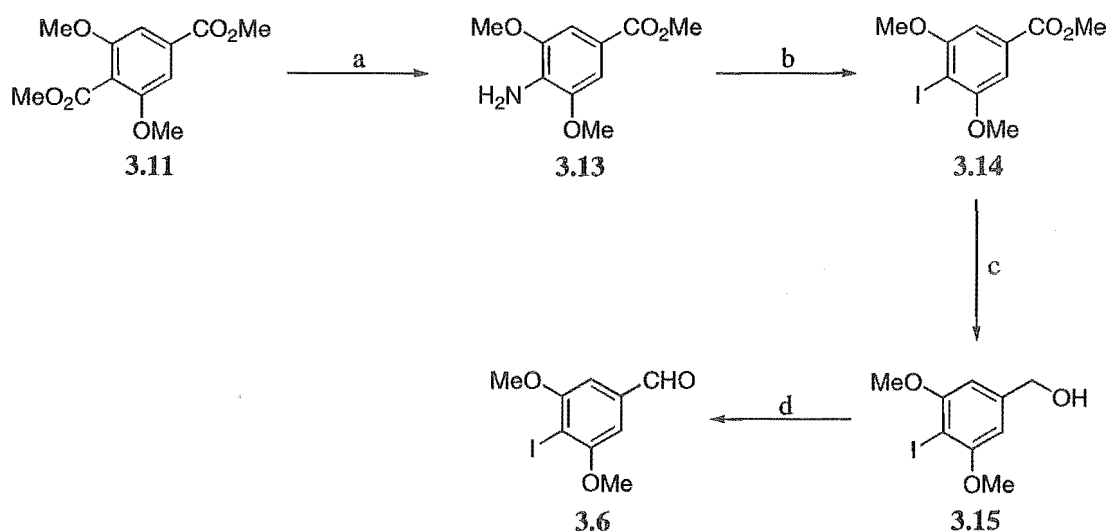
As discussed earlier, various halogenated derivatives of 3,5-dimethoxybenzaldehyde have been prepared starting from 2,6-dimethoxyterephthalate **3.11**. This enables useful functionality to be introduced and manipulated prior to formation of the heterocyclic moiety. Accordingly, the requisite phthalate **3.11** was prepared in 2 steps, beginning with a Kolbe-Schmitt carboxylation

of 3,5-dihydroxybenzoic acid, which gives diacid **3.12** as its mono-potassium salt in 62 % yield.⁸⁵ Gray *et al* reported that diacid **3.12** resisted methylation with potassium carbonate and iodomethane in acetone, which was presumably as a result of the insolubility of the potassium salt. It was found that the acid could be conveniently methylated using sodium hydride and iodomethane in *N,N*-dimethylformamide to give 2,6-dimethoxyterephthalate (**3.11**) in quantitative yield (Scheme 3.3).



Scheme 3.3 Reagents and yields: (a) KHCO_3 , glycerol, CO_2 , 180°C , 62 %; (b) NaH , DMF, MeI, r.t., 99 %.

The resulting phthalate **3.11** was readily converted into aldehyde **3.6** following the literature procedure (Scheme 3.4).⁸⁰ The permethylated compound **3.11** underwent a Lossen rearrangement on treatment with polyphosphoric acid and hydroxylamine to give amine **3.13** in 84 % yield. Iodide **3.14** was obtained in 85 % yield when amine **3.13** was reacted with NaNO_2/HCl , followed by potassium iodide. The resulting iodide **3.14** was readily reduced with diisobutylaluminium hydride in toluene to give alcohol **3.15** in quantitative yield. Finally, oxidation of alcohol **3.15** with manganese dioxide under Dean-Stark conditions gave aldehyde **3.6** in 89 % yield.



Scheme 3.4 Reagents and yields: (a) $(\text{NH}_2\text{OH})\cdot\text{H}_2\text{SO}_4$, PPA, 70°C , 84 %; (b) HCl , NaNO_2 , KI, 55°C , 85 %; (c) DIBAL, toluene, 0°C , 100 %; (d) MnO_2 , benzene, Dean-Stark, 89 %.

3.1.4 Investigation of the Palladium-catalysed Approach.

The reaction of propargylic compounds with organometallics under palladium catalysis is an interesting and useful reaction.⁸⁶ The catalytic cycle is shown in **Figure 3.13** and begins with an oxidative addition of the Pd^0 species to the propargyl halide.⁸⁷ The subsequent transmetalation reaction can proceed through either the allenylpalladium complex, formed by $\text{S}_{\text{N}}2'$ oxidative addition, or the propargylpalladium complex, formed by direct oxidative addition. Finally, reductive elimination gives either the propargyl or allenyl products.

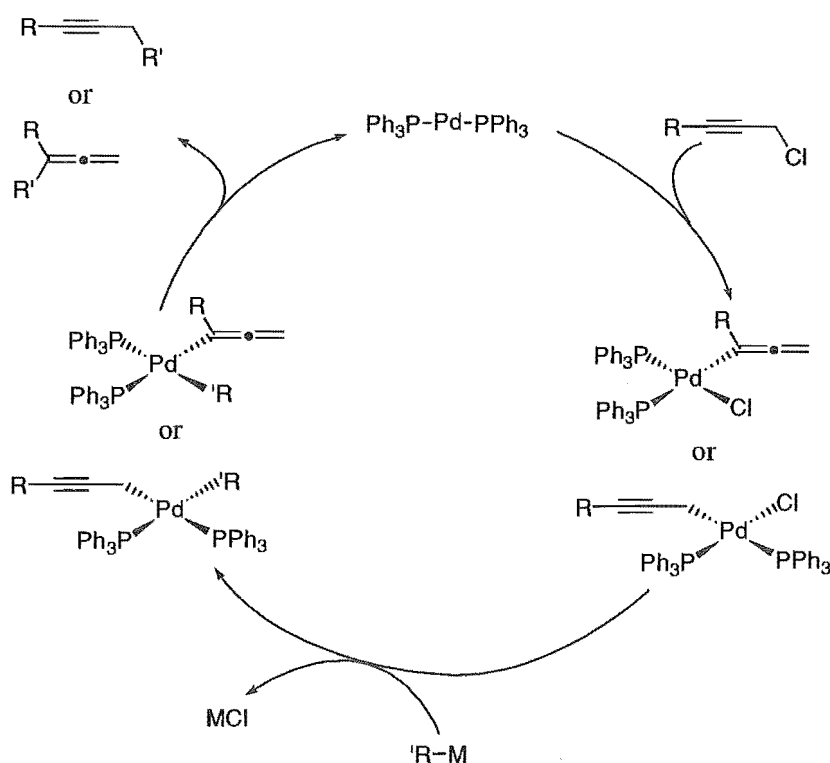


Figure 3.13 The catalytic cycle for palladium coupling of propargyl derivatives.

It is believed that the allenyl- and propargylpalladium complexes **3.16** and **3.17** exist in an equilibrium (**Figure 3.14**). The position of this equilibrium is governed by factors such as steric congestion. Therefore, for a large R group the equilibrium would be expected to favour the propargyl complex.

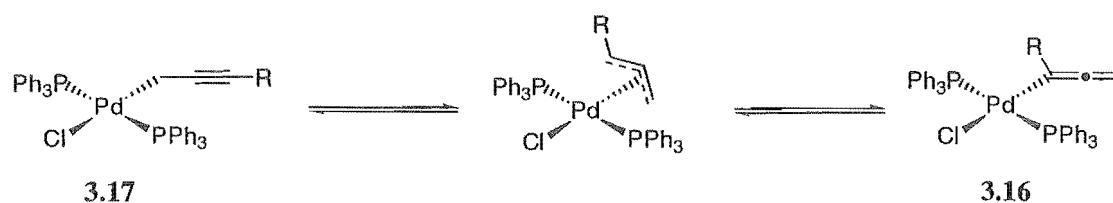
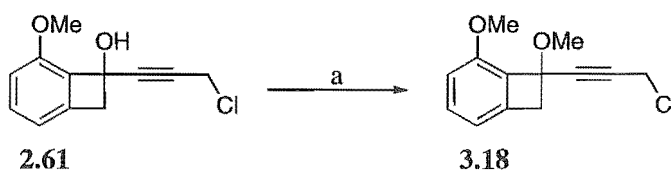


Figure 3.14 Equilibrium between propargyl and allenyl palladium complexes.

An appropriately functionalised propargyl chloride derivative **2.61** had already been prepared in Chapter 2. However, the alcohol proton of **2.61** could react with the organometallic coupling partner in the ensuing palladium coupling. Accordingly, the benzocyclobutenol **2.61** was protected as its methylether (**Figure 3.15**). Because of the potential sensitivity to base, the method of choice for protection of benzocyclobutenols is methylation using iodomethane and silver oxide.⁴⁶ Protection of benzocyclobutenol **2.61** using this method gave the ether **3.18** in 93 % yield.

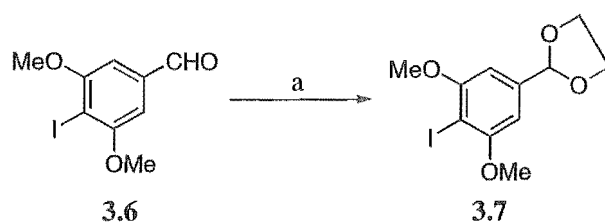


Reagents and yield: (a) Ag_2O , MeI, 93 %.

Figure 3.15 Protection of benzocyclobutenol **2.61**.

Due to the hindered nature of propargyl chloride **3.18**, upon oxidative addition, the equilibrium between the propargyl and allenyl intermediates would most likely favour the propargyl complex. Nonetheless, this was worthy of a short investigation as if it was successful it would provide rapid entry to the key cyclisation precursor.

Organozinc halides have been shown to be excellent participants in palladium-catalysed couplings of propargyl derivatives.⁸⁸ Before such an intermediate could be prepared, it was necessary to protect the aldehyde functionality of **3.6**. This was achieved by refluxing aldehyde **3.6** with 1,2-ethanediol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid to give acetal **3.7** in quantitative yield (**Figure 3.16**).



Reagents and yield: (a) 1,2-ethanediol, cat. TsOH, benzene, Dean-Stark, 99 %.

Figure 3.16 Protection of the aldehyde functionality.

Iodide **3.7** was lithiated with *t*-BuLi at $-95\text{ }^{\circ}\text{C}$, followed by addition of zinc chloride. The reaction was warmed slowly to room temperature, then propargyl chloride **3.18** and 5 mol % $\text{Pd}(\text{PPh}_3)_4$ were added and the reaction left for 24 h. Analysis of the ^1H NMR spectrum indicated the presence of several compounds. Column chromatography gave a number of fractions that were of use in interpreting the outcome of the reaction, see **Figure 3.18** on the next page. The initial fraction contained unreacted propargyl chloride **3.18** and what appeared to be allene **3.19**. The structure of the allene was based upon the similarity of its ^1H NMR spectrum to that of allene **2.63** prepared in Chapter 2. The next major fraction contained deiodinated acetal **3.20**. The final, and most interesting, fraction consisted of what appeared to be a mixture of coupled products and the ^1H NMR spectrum of this fraction is displayed in **Figure 3.17**.

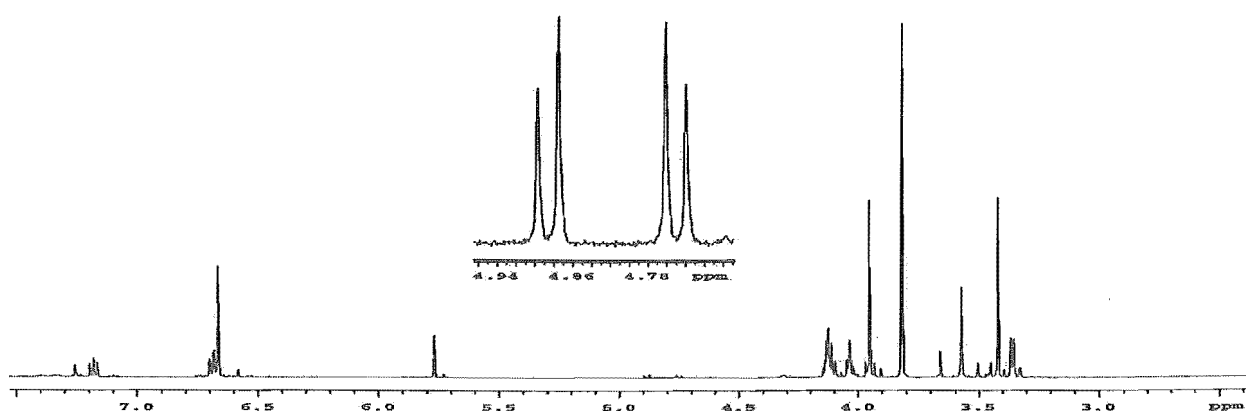
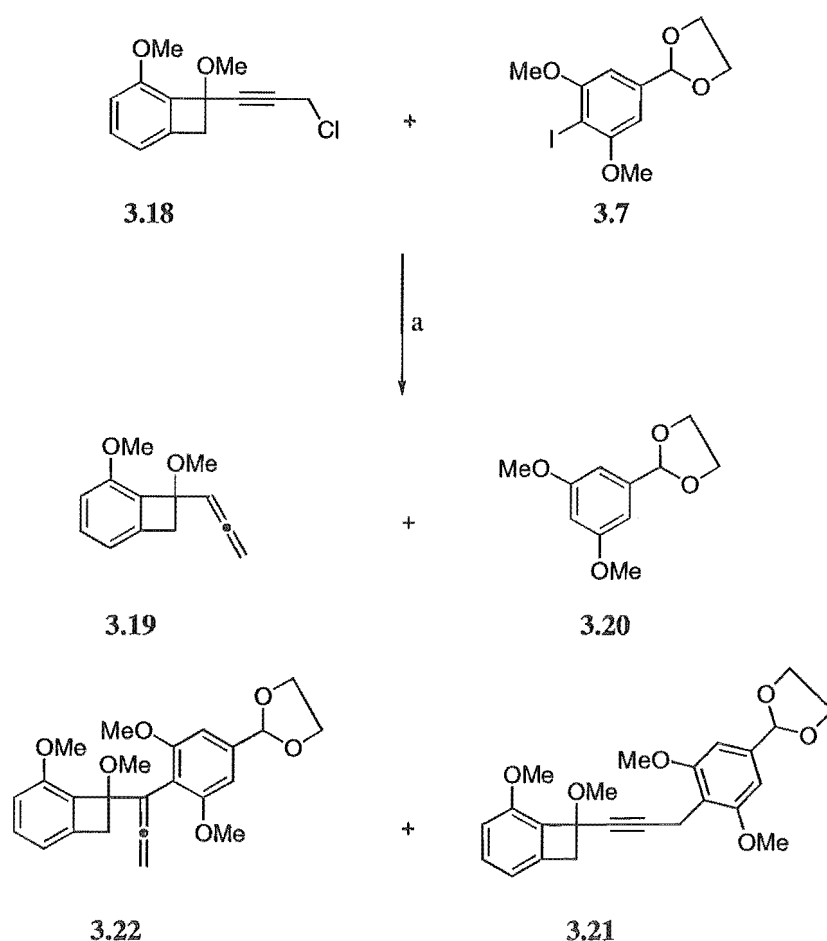


Figure 3.17 500 MHz ^1H NMR spectrum of the coupled products.

While these two compounds were unable to be separated, ^1H NMR analysis indicated that it was a mixture of acetylenic and allenic compounds **3.21** and **3.22**. Integration of the ^1H NMR

spectrum revealed a 9:1 ratio in favour of the acetylenic alcohol, as was expected on steric grounds. It is believed that the sterically demanding nature of both the propargyl chloride and the arylmetal species dictate that the major coupling product from this reaction is that formed from reductive elimination of the propargylpalladium intermediate. It was seen as unlikely that this equilibrium could be perturbed so as to produce predominantly the allenic species. Accordingly, this approach was deemed unsuitable in terms of an efficient synthesis of the sterically demanding 1,1'-disubstituted allene 3.22.



Reagents and conditions: (a) *t*-BuLi, ZnCl₂, THF, -95 °C to r.t., then 5 mol % Pd(PPh₃)₄ and 3.18.

Figure 3.18 Products from the palladium coupling.

3.1.5 Attempted Synthesis of Allenyllithium Precursors

An alternative approach for the synthesis of an allenic alcohol such as **3.1** is the addition of an allenyllithium species to benzocyclobutenone **2.12**. It was envisaged that a precursor to allenyllithium **3.23** could be derived from an acetylene **3.24** such as by an S_N2' reduction as shown below (Figure 3.19). Subsequent lithiation of allene **3.25** at the non-terminal position⁸⁹ would give allenyllithium **3.23**.

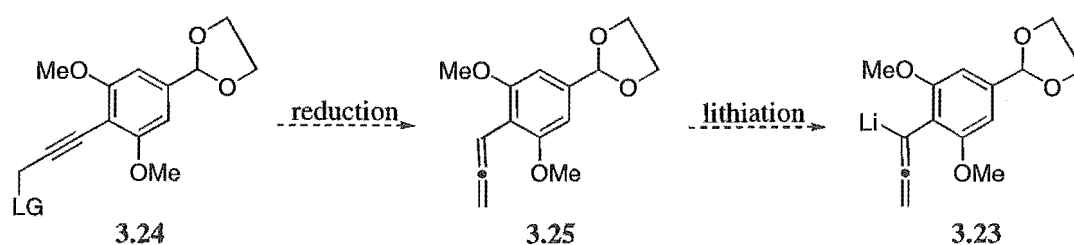


Figure 3.19 A possible route to allenyllithium **3.23**.

Introduction of an acetylene moiety could be achieved by a Sonogashira coupling.⁸¹ This reaction involves the coupling of terminal acetylenes with aryl or vinyl halides, in the presence of palladium complexes and copper salts (Figure 3.20).

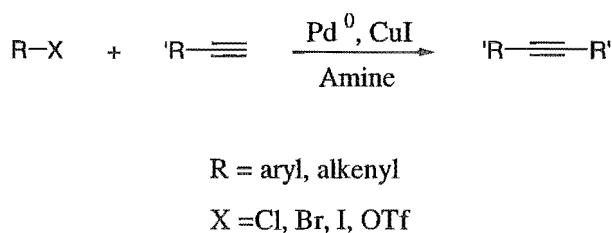
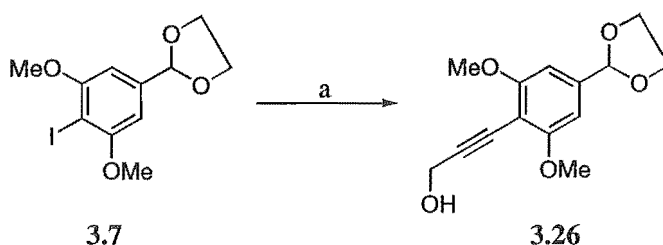


Figure 3.20 Sonogashira coupling.

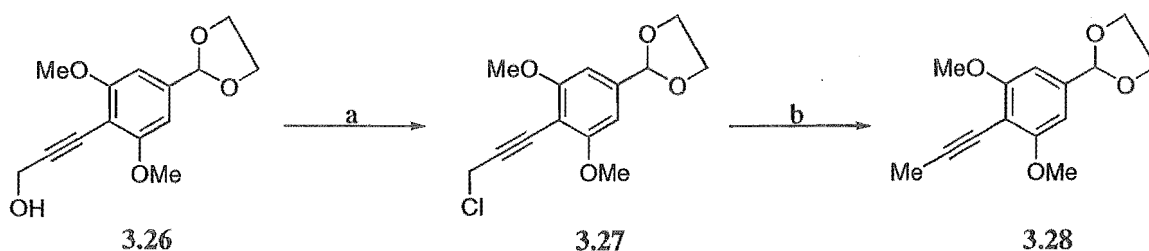
As a result of the hindered nature of iodide **3.7** the reaction would be expected to be slow under the standard conditions. However, Alami *et al* have shown that pyrrolidine is an excellent solvent for Sonogashira couplings, given that it results in faster reaction times and superior yields compared to a variety of other amines.⁹⁰ Propargyl alcohol was chosen as the initial coupling partner as it was envisaged that the alcohol group could be converted into an

appropriate leaving group for a forthcoming S_N2' reduction. Treatment of iodide **3.7** with propargyl alcohol, 10 mol % CuI, and 5 mol % $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in pyrrolidine at room temperature for 3 hrs resulted in no reaction. In contrast, heating the reaction at reflux resulted in the formation of a new product as shown by TLC. Continued heating gave no further conversion to product. Analysis of the crude reaction workup by ^1H NMR spectroscopy confirmed a mixture of starting material and a new product. Chromatography gave the desired acetylene **3.26** in 44 % yield. It was subsequently found that increasing the loading of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ from 5 mol % to 7.5 mol % resulted in complete consumption of starting material and isolation of the pure product in 79 % yield (Scheme 3.5).



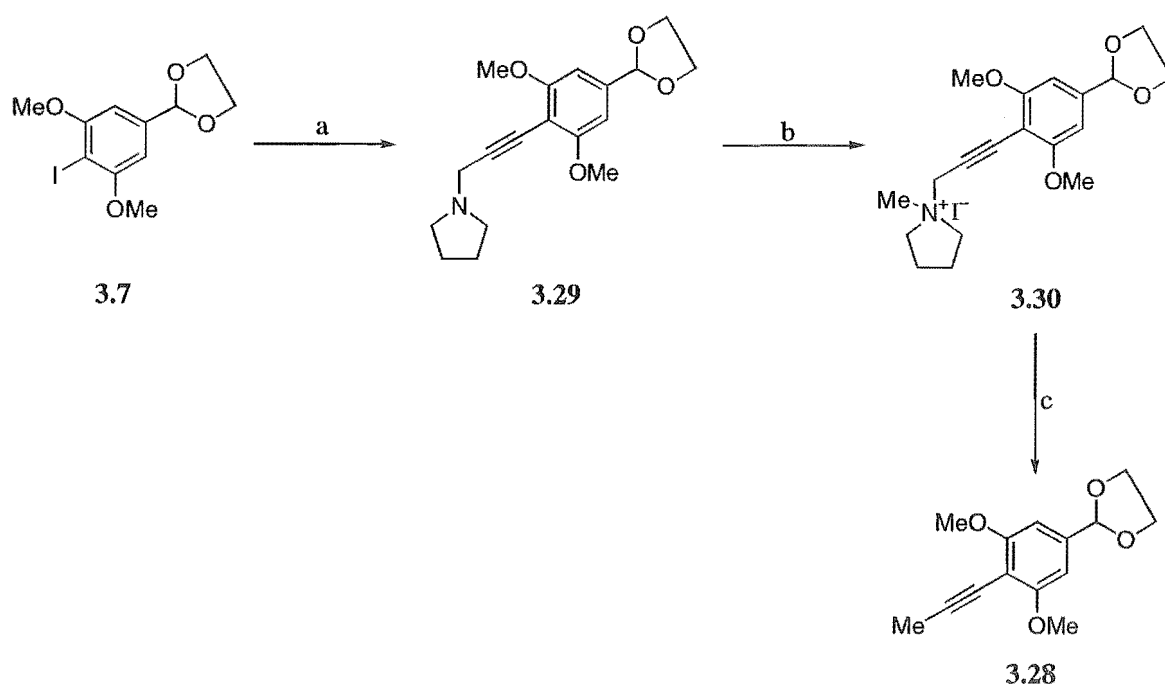
Scheme 3.5 Reagents and yield: (a) 7.5 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, 10 mol % CuI, propargyl alcohol, pyrrolidine, 79 %.

Conversion of the propargyl alcohol derivative **3.26** into an appropriate precursor for an S_N2' reduction was readily achieved under the conditions developed by Nicolaou *et al.*⁹¹ Reaction of alcohol **3.26** with *p*-toluenesulfonyl chloride, triethylamine, and *N,N*-dimethylaminopyridine in dichloromethane gave chloride **3.27** in 68 % yield. Unfortunately, reduction of chloride **3.27** with lithium aluminium hydride gave only propyne **3.28** as a result of a reduction in an S_N2 fashion, rather than in a S_N2' fashion. (Scheme 3.6).



Scheme 3.6 Reagents and Yields: (a) TsCl, NEt_3 , DMAP, CH_2Cl_2 , r.t., 68 %; (b) LiAlH_4 , THF, r.t.

It has been shown that the quaternary ammonium group is a superior leaving group for the selective formation of allenes from propargylic acetylenes.⁹² It was envisaged that a precursor to a quaternary ammonium group could be prepared in a one pot Sonogashira coupling. If propargyl chloride was used as the coupling partner, then under the reaction conditions it could be expected that pyrrolidine would displace the chloride, yielding a propargyl amine. Indeed, reaction of propargyl chloride with aryl iodide **3.7**, under Sonogashira conditions in pyrrolidine at reflux, gave amine **3.29** in 80 % yield. Treatment of amine **3.29** with iodomethane in acetone gave quaternary ammonium salt **3.30** in 93 % yield (**Scheme 3.7**). Unfortunately, reduction of the ammonium salt with LiAlH_4 in THF gave predominantly acetylene **3.28**. Again, the sterically hindered nature of the aromatic moiety dictates that the hydride would be delivered in an $\text{S}_{\text{N}}2$ fashion, resulting in the formation of an acetylene, as opposed to delivery in an $\text{S}_{\text{N}}2'$ fashion, which would result in allene formation.



Scheme 3.7 Reagents and yields: (a) Propargyl chloride, pyrrolidine, 7.5 mol % $\text{Pd(PPh}_3)_2\text{Cl}_2$, 10 mol % CuI , reflux, 80 %. (b) MeI , acetone, r.t., 93 %; (c) LiAlH_4 , THF, r.t.

In order to overcome this problem a reaction that would favour formation of the more sterically hindered product was required. Yamamoto *et al* have demonstrated an example of such a reaction. It was shown that propargyl stannane **3.31** could be isomerised to give the more hindered allenyl stannane **3.32** in quantitative yield using $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as the catalyst

(Figure 3.21).⁹³ It was felt that this methodology could be adapted to provide a useful precursor to allenyllithium 3.23.

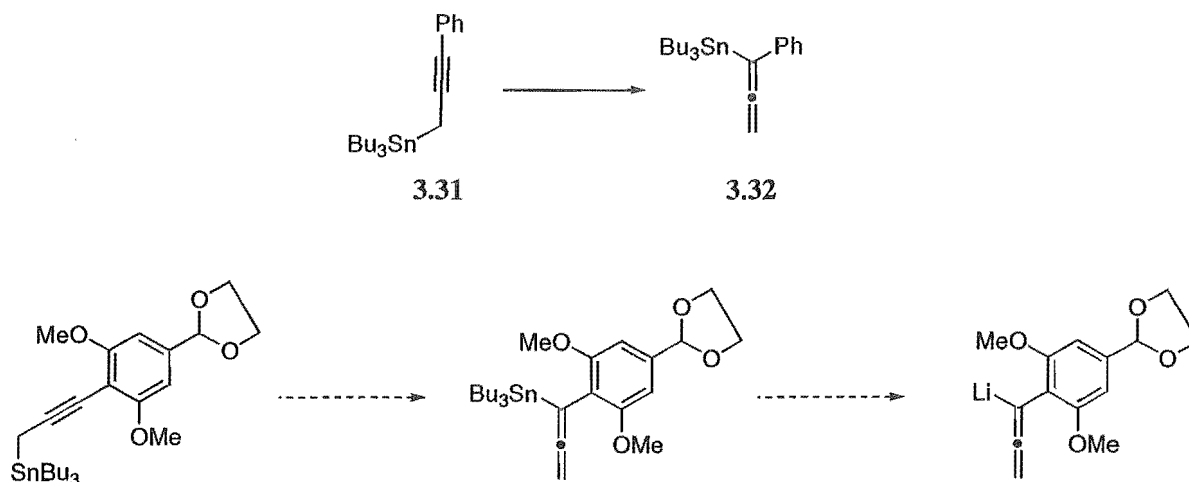


Figure 3.21 Isomerisation of propargylstannanes.

It was hoped that this could be accomplished by a one-pot reaction of hexabutylditin with chloride 3.27 and a palladium catalyst. However, treatment of chloride 3.27 with either $\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}_2(\text{dba})_3$, and hexabutylditin gave only propargylstannane 3.33 in poor yield (Figure 3.22).

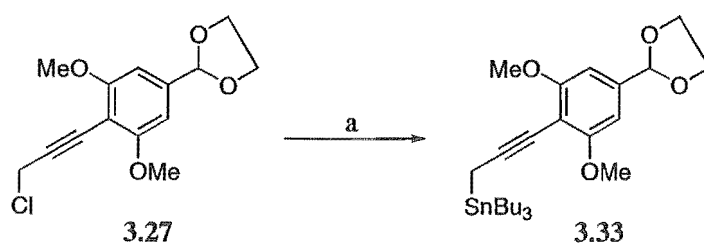


Figure 3.22 Reagents and yield: (a) $\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}(\text{dba})_3$, $(\text{Bu}_3\text{Sn})_2$, THF, reflux, 13-40 %.

3.1.6 Summary and Conclusions

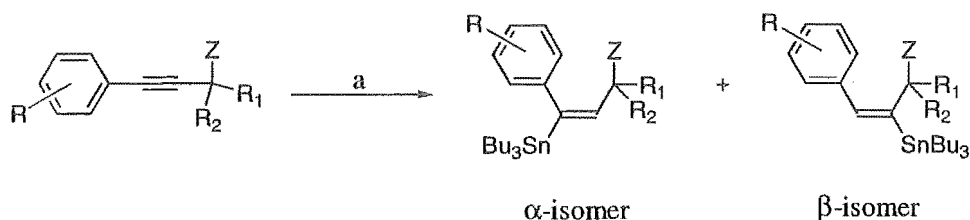
A synthetic approach to ancistrocladidine was designed which would proceed *via* an allenic alcohol, which could be thermolysed to give the appropriate naphthol. This allenic species could either contain the entire heterocyclic moiety or a precursor to the heterocyclic moiety. However, attempted functionalisation of 3,4-dihydroisoquinoline derivative between the methoxy groups by directed *ortho*-metalation procedures proved fruitless. Accordingly, a precursor was prepared where an iodide group was already placed between the methoxy groups.

Two approaches were outlined for the synthesis of the key allenic alcohol. The first of these involved a palladium-catalysed coupling between an arylzinc reagent and chloride **3.18**. Unfortunately, due to the sterically demanding nature of both the chloride and the arylzinc reagent, the major coupling product from this reaction was the less hindered propargyl product **3.21**, not the desired allenyl product **3.22**. The second approach to allenic alcohol involved addition of an allenyllithium species to benzocyclobutenone **2.12**. Unfortunately, no such allenyl lithium precursor could be prepared. Firstly, an attempted S_N2' reduction, to form an allene, resulted only in a more sterically favoured S_N2 reduction, which gave acetylene **3.28**. Following this, a reaction involving isomerisation of a propargyl stannane was attempted. However, the only product isolated from this reaction was, again, the less hindered species propargyl stannane **3.33**.

3.2 An Approach Based on an Alkenylbenzocyclobutenol

3.2.1 Introduction

In the search for reactions that would yield an appropriately functionalised organometallic species, a hydrometalation procedure described by Alami *et al* was of particular interest (Figure 3.23).⁹⁴ The reaction involves the palladium-catalysed hydrostannylation of arylacetylenes. This reaction shows excellent regioselectivity forming the α -isomers for arylalkynes with electron accepting groups in the *para*-position, or groups of any electronic nature in the *ortho*-position.



Reagents and conditions: (a) 1 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, HSnBu_3 , THF, r.t.

Figure 3.23 Alami *et al.*'s hydrostannylation.

Interestingly, the α -selectivity of this reaction was enhanced by increasing the steric bulk at the *ortho*-position, with an *ortho*-disubstituted aromatic group giving exclusively the α -isomer (Figure 3.24). Using this procedure it is possible that the *ortho*-disubstituted dihydroisoquinoline precursor **3.26** could undergo a hydrostannylation to give the desired α -isomer **3.34**.

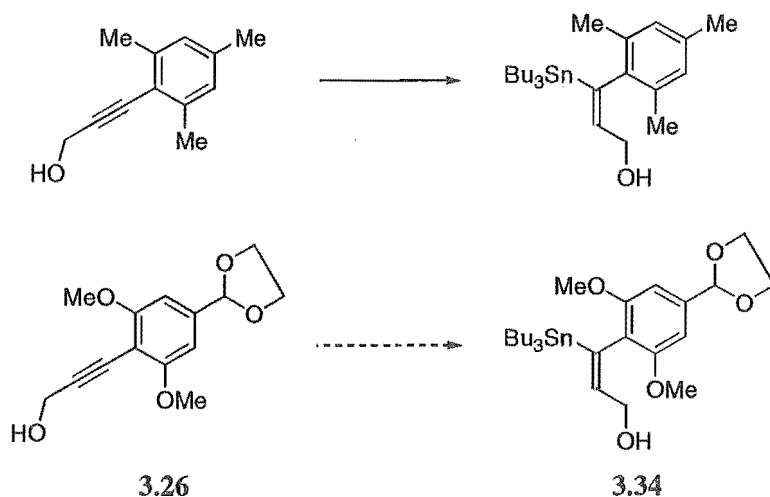


Figure 3.24 A possible hydrostannylation of acetylene **3.26**.

In order to incorporate this procedure into a synthetic approach to ancistrocladidine, the work of Wallace *et al* needs to be revisited.⁴⁶ It was shown that a variety of substituted organometallics could be added to benzocyclobutenones and thermolysis of these adducts provided an efficient route to substituted tetralones (Figure 3.25). Of particular interest is the addition of α -styryl

Grignard reagents which gave the benzocyclobutenol **3.35**. Cyclisation of this adduct gave the respective tetralone **3.36** in 71 % yield.

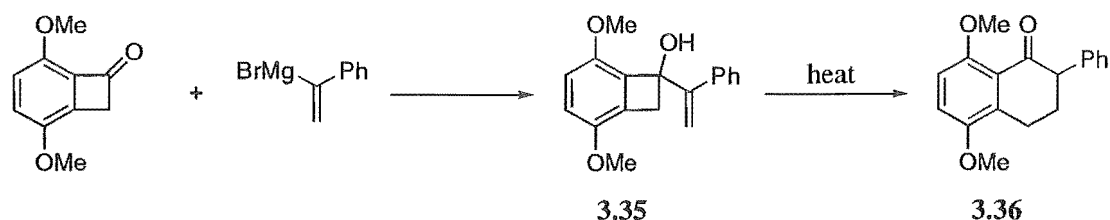


Figure 3.25 Wallace *et al*'s synthesis of tetralones.

This was potentially useful because the position of the aromatic substituent in tetralone **3.36** relates to the position of the dihydroisoquinoline moiety in ancistrocladidine. As detailed in **Figure 3.26**, a synthesis of ancistrocladidine could be developed using this chemistry. If the appropriate stannane **3.34** could be generated, using Alami's procedure, it could be reacted *via* transmetalation, with benzocyclobutenone **2.12**. Thermolysis of the resulting benzocyclobutenol should give tetralone **3.37**, which upon aromatisation would give naphthol **3.38**. The dihydroisoquinoline entity could then be annealed onto naphthol **3.38** to give a synthesis of the natural product.

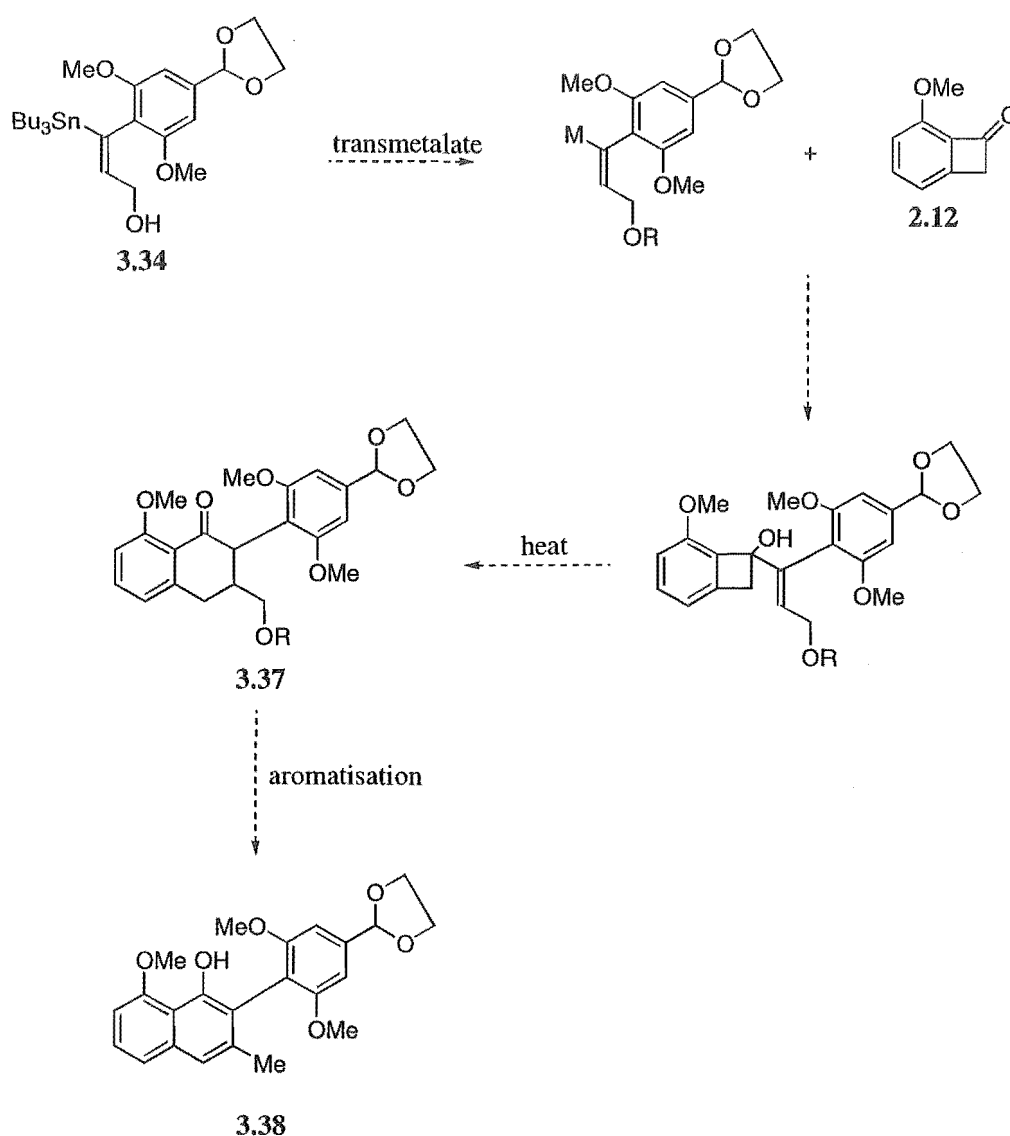
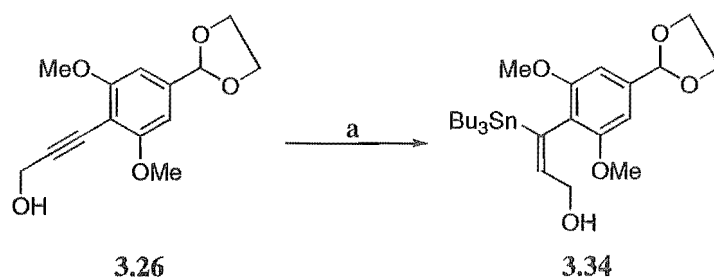


Figure 3.26 An approach to naphthol 3.38.

3.2.2 Initial Hydrostannylation Studies

As the requisite acetylene 3.26 had been synthesised for earlier studies, the hydrostannylation procedure could be explored on this substrate. Reaction of acetylene 3.26 with tributyltin hydride and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in THF for 10 min at room temperature resulted in complete consumption of starting material. Analysis of the ^1H NMR spectrum of the crude product indicated the presence of only one isomer. Purification by column chromatography gave a single compound, stannane 3.34, in a pleasing 90 % yield (Figure 3.27).



Reagents and yield: (a) 1 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, HSnBu_3 , THF, r.t., 90 %.

Figure 3.27 Successful hydrostannylation of acetylene **3.26**.

The regioselectivity of this reaction can be confirmed by examination of the ^1H NMR spectrum of this compound (**Figure 3.28**). The coupling pattern of the olefinic proton at δ 6.14 ppm, which appears as a triplet of triplets, is consistent with the olefinic proton being coupled to both tin and the allylic methylene protons.

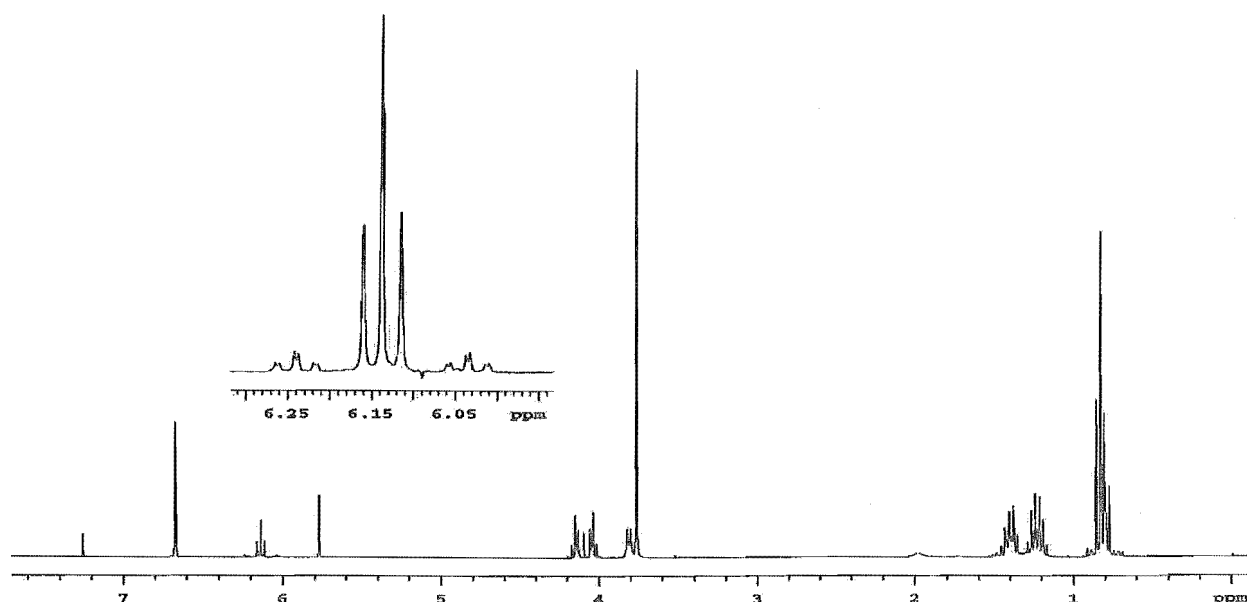


Figure 3.28 300 MHz ^1H NMR spectrum of stannane **3.34**.

This regioselective formation of stannane **3.34** was a pleasing result given the sterically demanding nature of such a reaction. Efforts could now be focused on an appropriate transmetalation reaction to form an organometallic species capable of reacting with the benzocyclobutenone **2.12**.

3.2.3 Formation of a Lithiospecies

Transmetalation is a useful reaction for interconversion between different organometallics, which have differing reactivity.⁹⁵ For example, organostannanes are of insufficient reactivity to form carbon-carbon bonds upon exposure to ketones under normal conditions, but are capable of undergoing transmetalation to organolithium species⁹⁶, which readily react with ketones under mild conditions. In general, transmetalation involves transfer of an R group from a main group organometallic (M) to another metal (M') (Figure 3.29).



Figure 3.29 Generalised transmetalation reaction.

As the above reaction is an equilibrium, transmetalation tends to be favoured when the more electropositive metal becomes bound to the more electronegative group. It is for this reason that alkenylstannanes are readily lithiated by alkyllithium reagents, as lithium, the more electropositive metal, becomes bound to the sp^2 -hybridised carbon atom, which is more electronegative than the sp^3 -hybridised carbon atom of an alkyl group.

As stannane **3.34** is of insufficient reactivity to form a bond upon exposure to benzocyclobutenone **2.12**, it must be transformed into a more reactive species. As seen in Chapter 2, organolithium species react readily with benzocyclobutenones, so lithiation of stannane **3.34** was of interest. While the alcohol proton would be readily deprotonated upon treatment of **3.34** with an alkyllithium reagent, it was believed that transmetalation could still take place if 2 equivalents of alkyllithium were used (Figure 3.30). Upon addition of alkyllithium reagents to stannane **3.34** a cloudy solution was observed. Quenching of the reaction with water gave only recovered starting material. It was postulated that insolubility of the deprotonated alcohol was hindering the desired lithiation of **3.34**.

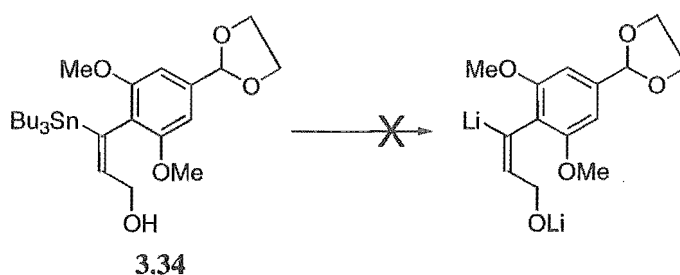
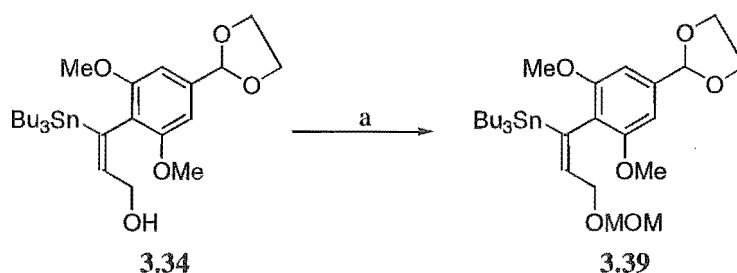


Figure 3.30 Attempted lithiation of stannane 3.34.

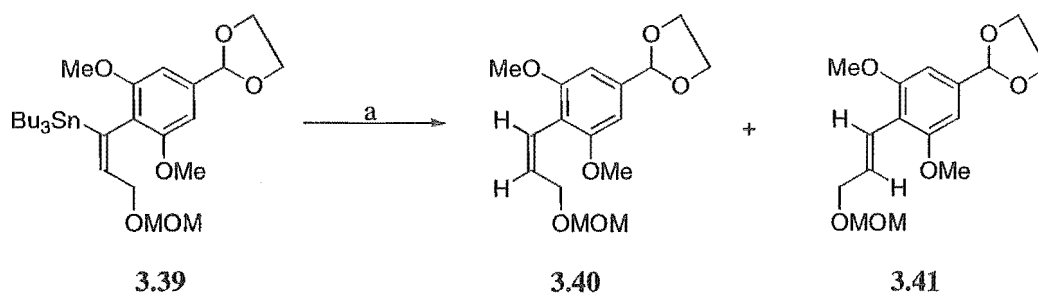
In order to increase the likelihood of transmetalation, the alcohol was protected as its methoxymethyl ether by treating alcohol 3.34 with methoxymethyl chloride and Hünig's base in dichloromethane (**Figure 3.31**).⁹⁷



Reagents and yield: (a) MOM-Cl, Hünig's base, CH_2Cl_2 , 0 °C to r.t., 100 %.

Figure 3.31 Protection of alcohol 3.34 as its methoxymethyl ether.

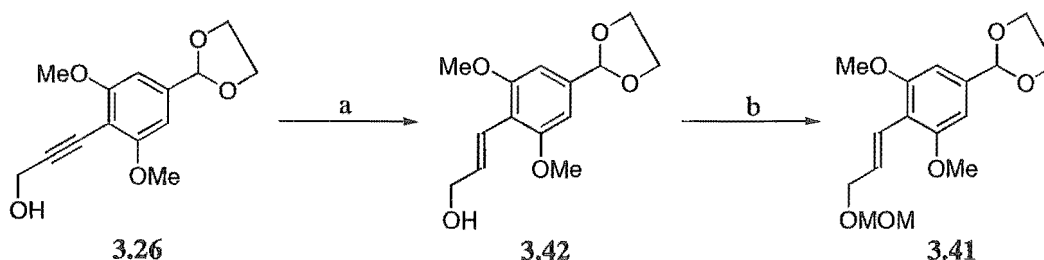
After experimentation with various alkyl lithium reagents (*n*-BuLi, *t*-BuLi, MeLi), solvents (Et_2O , THF), and reaction temperatures, it was found that stannane 3.39 could be lithiated by treatment with MeLi at – 60 °C in THF. Quenching of the lithiospecies with water gave two compounds, which could not be separated by conventional chromatography. From examination of the ^1H NMR spectrum of these compounds it was postulated that they were the isomeric alkenes 3.40 and 3.41 shown below (**Figure 3.32**).



Reagents and conditions: (a) MeLi, THF, -60°C , aq NH_4Cl .

Figure 3.32 Formation and quenching of the lithiospecies resulting in a mixture of **3.40** and **3.41**.

The presence of the (E)-alkene **3.41** was surprising, so to confirm the above structural elucidation an authentic sample of (E)-isomer **3.41** was prepared as detailed in **Scheme 3.8**. Reduction of acetylene **3.26** with lithium aluminium hydride in THF gave (E)-allylic alcohol **3.42**, which was converted to methoxymethyl ether **3.41** by reaction with methoxymethyl chloride and Hünig's base in dichloromethane.



Scheme 3.8 Reagents and yield: (a) LiAlH_4 , THF, r.t.; (b) MOM-Cl, Hünig's base, CH_2Cl_2 , 0°C to r.t., 65 % over 2 steps.

Comparison of the ^1H NMR spectrum of (E)-isomer **3.41** with that of the mixture of compounds, showed that indeed the (E)-isomer was one of these compounds (**Figure 3.33**).

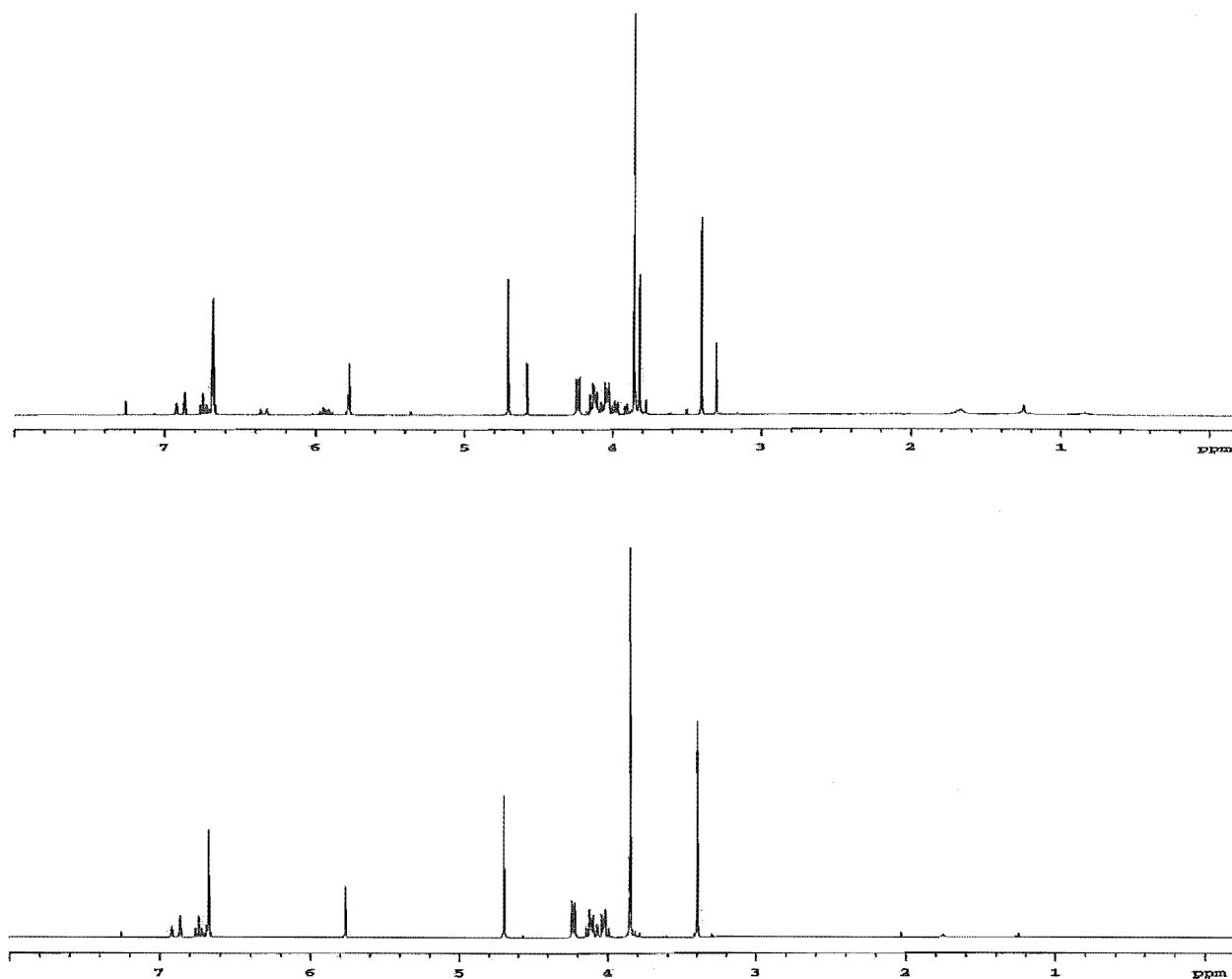
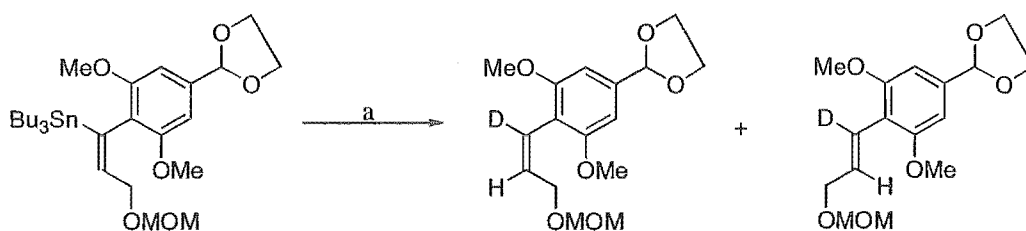


Figure 3.33 300 MHz ^1H NMR spectra of pure (E)-isomer **3.41** (bottom), and of the mixture of isomers **3.40** and **3.41** (top).

In order to ensure some sort of rearrangement of the lithiospecies wasn't occurring, and also to ensure the lithiospecies wasn't being quenched *in situ*, a deuterium quench was conducted. Generation of the lithiospecies, as previously described, followed by quenching the reaction with CD_3OD afforded the same mixture of as above, with ^1H NMR analysis indicating that deuterium had been incorporated into the expected positions (**Figure 3.34**). This established the stability of the lithiospecies under the reaction conditions and confirmed that transfer of lithium to another position wasn't occurring.



Reagents and conditions: (a) MeLi, THF, -60 °C, CD₃OD.

Figure 3.34 Deuterium quenching experiment.

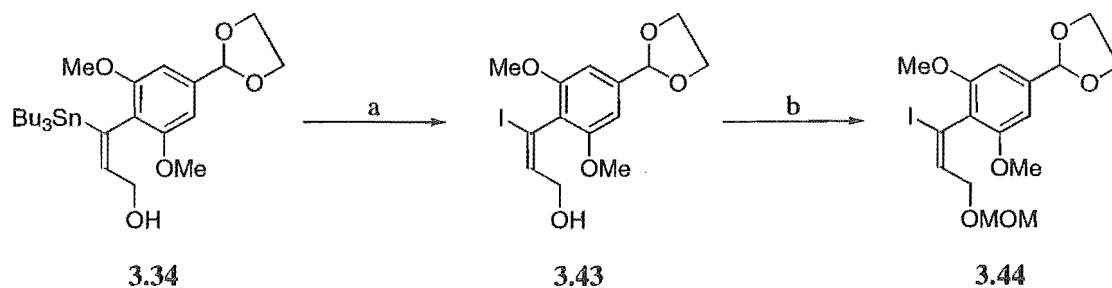
Although quenching of the lithiospecies resulted in formation of isomers, this loss of stereochemical integrity wouldn't matter in terms of a projected total synthesis of ancistrocladidine. The reason for this is both carbons of the isomerised double bond become part of the naphthalene ring in the natural product, resulting in the loss of any elements of stereochemistry upon aromatisation.

3.2.4 Studies on the Reaction of Alkenyllithiospecies with 6-Methoxybenzocyclobutenone

Reaction of the derived lithiospecies with benzocyclobutenone **2.12** was now of interest. A solution of the benzocyclobutenone **2.12** was added to a solution of the lithiospecies, generated as described above, and the reaction stirred for 2 h at -60 °C. Analysis by TLC indicated that no new products were being generated. The solution was warmed to -25 °C over a period of 2 h, following which the reaction was worked up. Analysis of the ¹H NMR spectrum of the crude workup showed only unreacted starting material **2.12** and the alkene mixture **3.40** and **3.41**. Repeating the reaction, but allowing it to warm slowly to room temperature gave a similar result.

Some thought was required about the lack of reactivity of benzocyclobutenone **2.12** towards the organolithium species. A product arising from transmetalation of tributylstannanes with methyllithium is tributylmethylstannane. As this species is rather bulky, its presence in solution could be interfering with the desired reaction, and so it was decided to compare the reactivity of a lithiospecies derived from iodide **3.44**. This was obtained in two steps from stannane **3.34** by stirring with iodine in dichloromethane, followed by protection using the previously developed

conditions. (Scheme 3.9). Halogen /metal exchange of the resulting iodide proceeded smoothly upon treatment with *t*-BuLi at $-78\text{ }^{\circ}\text{C}$ in THF. Addition of ketone **2.12**, followed by slow warming of the reaction failed to afford any desired product.

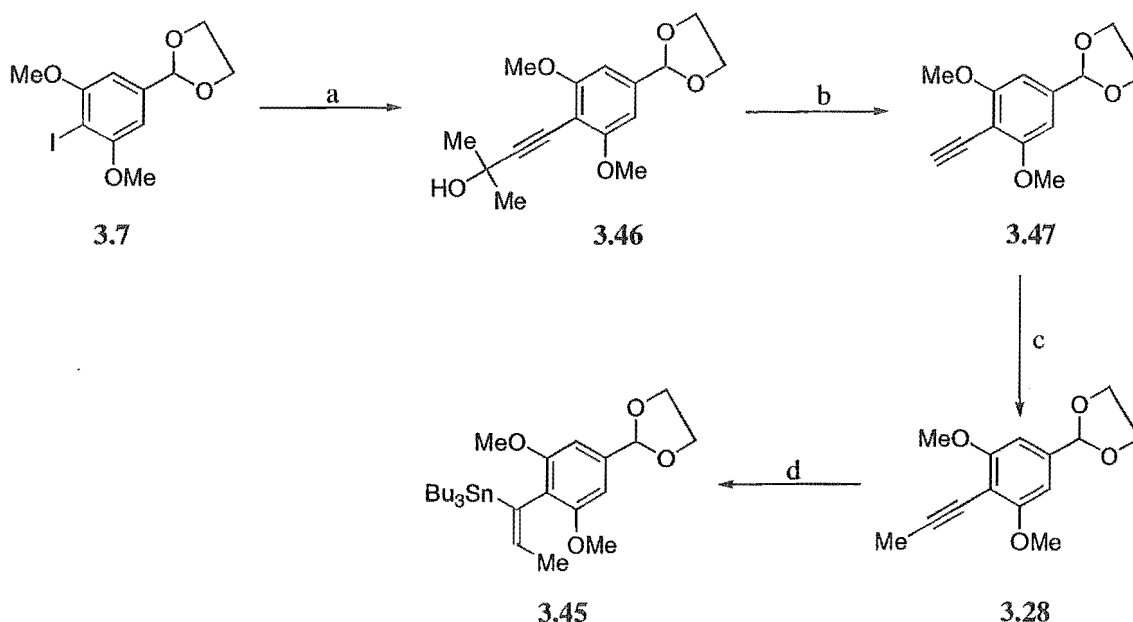


Scheme 3.9 Reagents and yields: (a) I_2 , CH_2Cl_2 , r.t., 84 %; (b) MOM-Cl, Hünig's base, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ to r.t., 100 %.

As the methoxymethyl group is a known director of *ortho*-lithiation,⁹⁸ it is possible that this group is co-ordinating to the lithium by an intermolecular process thereby producing a very hindered nucleophile that is incapable of reacting with the benzocyclobutenone. Addition of HMPA is known to increase the reactivity of organolithium reagents by lowering the degree of aggregation and increasing reactivity through cation coordination.⁹⁹ Accordingly, addition of HMPA to the above reaction could decrease the steric bulk of the lithiospecies, thereby increasing its reactivity toward the benzocyclobutenone. Unfortunately, reaction of the lithiospecies with benzocyclobutenone **2.12** in THF/HMPA (4:1), starting at $-60\text{ }^{\circ}\text{C}$ and warming to $-10\text{ }^{\circ}\text{C}$ over 4 hours, gave a complex mixture of products from which none of the desired product could be isolated.

In the initial synthetic approach it was envisaged that the methyl group, contained in the natural product, would not be generated until the aromatisation step. However, on account of the complicating issue associated with the methoxymethyl protecting group it was decided to investigate the preparation and reaction of an alternative lithiospecies that contained the methyl group, instead of the methoxymethyl group. The requisite stannane **3.45** was prepared as described in Scheme 3.10. Sonogashira coupling of iodide **3.7** with 2-methyl-3-butyne-2-ol gave arylacetylene **3.46** in 87 % yield. Deprotection of this acetylene with sodium hydroxide in refluxing toluene gave terminal acetylene **3.47** in 95 % yield. Subsequent methylation with *n*-BuLi/iodomethane in THF gave propyne **3.28** in 51 % yield. Pleasingly, hydrostannylation of

3.28 proceeded with excellent regioselectivity, affording stannane 3.45, in 87 % yield after chromatography.

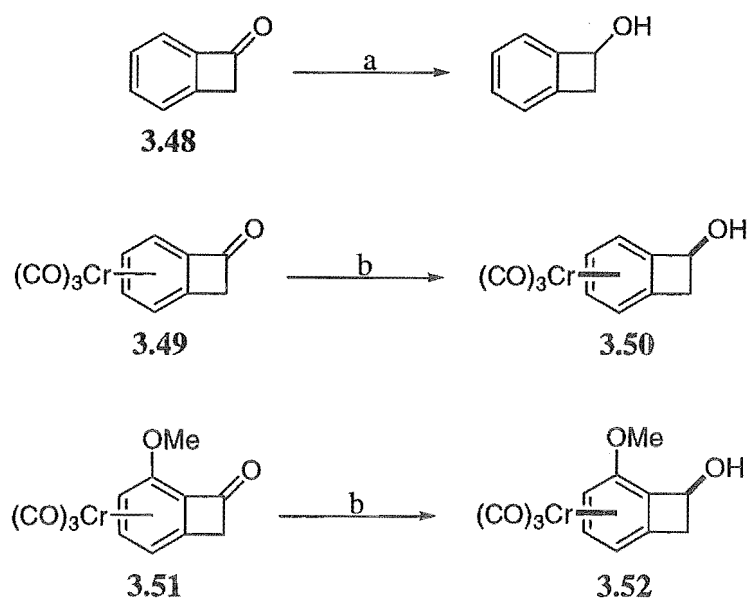


Scheme 3.10 Reagents and yields: (a) 2-Methyl-3-buten-2-ol, 7.5 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, 10 mol % CuI , pyrrolidine, reflux, 87 %; (b) NaOH , toluene, reflux, 95 %; (c) $n\text{-BuLi}$, THF, 0 °C, MeI , r.t., 51 %; (d) 1 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, HSnBu_3 , THF, r.t., 87 %.

Attempted lithiation of stannane 3.45 under the previously described conditions gave only recovered starting material. However, it was found that the stannane could be lithiated by treatment with MeLi in diethyl ether at room temperature. Cooling of this solution to $-60\text{ }^\circ\text{C}$, followed by addition of a solution of the benzocyclobutenone in THF resulted in a mixture of compounds from which only the benzocyclobutenone and destannylated materials were recovered after chromatography. Thus, altering the functionality present in the lithiospecies failed to give any of the desired adduct, so attention was turned to altering the reactivity of the benzocyclobutenone.

3.2.5 Synthesis and Reactivity of a Chromium Complex of 6-Methoxybenzocyclobutenone

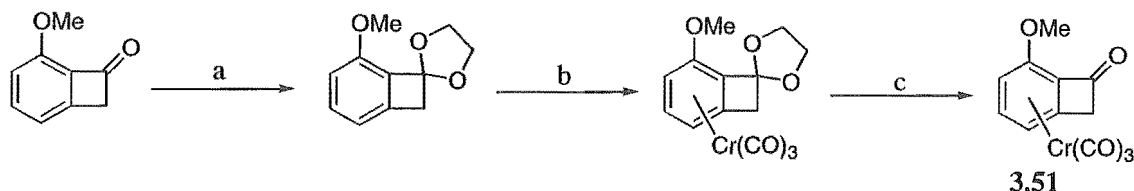
Arenes form stable, isolable complexes with chromium.¹⁰⁰ Arenechromium tricarbonyl complexes are of the η^6 -coordination type, which means the entire π -system of the aromatic moiety is complexed. This has far-reaching implications in terms of the change in reactivity observed in the complexed arene, in comparison to the uncomplexed arene. Indeed, chromium complexes of benzocyclobutenones are known and such a complex of benzocyclobutenone **2.12** has been reported.¹⁰¹ The coordination of tricarbonylchromium leads to a noticeable increase in reactivity of the keto group of benzocyclobutenones. This has been attributed to the rigidity of the anellated cyclobutenone ring, which allows optimum transfer of the electron withdrawing effect of the tricarbonylchromium group to the ketone carbonyl atom. For example, in the related desmethoxy system, reduction of the uncomplexed benzocyclobutenone **3.48** proceeds in 83 % yield after refluxing with lithium aluminium hydride in ether. In contrast, the tricarbonylchromium complex **3.49** is reduced immediately upon treatment with lithium aluminium hydride at -78°C , in the same solvent, to give benzocyclobutenol **3.50** in 99 % yield and 99 % de.¹⁰² Reduction of complex **3.51** proceeds with similar ease giving the benzocyclobutenol **3.52** in 98 % yield (Figure 3.35).



Reagents and yields: (a) LiAlH_4 , Et_2O , reflux, 83 %; (b) LiAlH_4 , Et_2O , -78°C , quantitative.

Figure 3.35 Comparative reactivity of benzocyclobutenones.

It was expected that chromium complex **3.51** would show a greater affinity for reaction with a lithiospecies and this was the next avenue of investigation. Chromium complex **3.51** was synthesised according to the literature procedure outlined in **Scheme 3.11**.¹⁰¹



Scheme 3.11 Reagents and yields: (a) 1,2-Ethanediol, cat. TsOH, benzene, Dean-Stark, 74 %; (b) Cr(CO)_6 , $\text{Bu}_2\text{O/THF}$, reflux, 81 %; (c) Conc HCl, r.t., 98 %.

The yield for the complexation reaction was somewhat lower than that reported in the literature and this has been attributed to the presence of *p*-xylene in the dibutyl ether from some commercial sources.¹⁰³ However, sufficient quantities of pure complex were obtained, but in order to get a satisfactory ^1H NMR spectrum of complex **3.51** it was necessary to filter the sample through a small plug of silica directly into the NMR tube, under inert conditions in the absence of light. This is because when chromium complexes are in solution, exposure to light can cause oxidative demetalation.¹⁰⁴ This in turn can lead to very poorly resolved spectra.

With pure complex **3.51** in hand, its reaction with the lithiospecies derived from stannanes **3.39** and **3.45** were investigated. In spite of many attempts, no adducts could be isolated from the reaction between the chromium complex and the lithiospecies derived from either stannane **3.39** or **3.45**. Variation of the solvent, temperature, and addition of HMPA resulted only in demetalated products being isolated.

In order to determine whether either of the derived lithiospecies were capable of reacting with a carbonyl group, a reaction was conducted between the lithiospecies derived from **3.39** and *m*-methoxybenzaldehyde. Generation of the lithiospecies as previously described, followed by addition of *m*-methoxybenzaldehyde at $-60\text{ }^\circ\text{C}$, resulted in complete consumption of starting material within 10 min. The reaction was worked up and the tin residues were removed by chromatography to give a product whose ^1H NMR spectrum indicated was a mixture of diastereoisomers as shown in **Figure 3.36**.

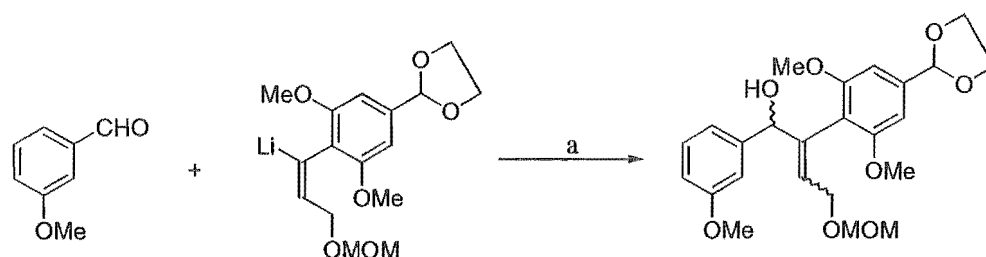


Figure 3.36 Reaction of a lithiospecies with *m*-methoxybenzaldehyde.

This indicated that the lack of reactivity of the lithiospecies, towards the benzocyclobutenone, was not as a result of the lack of reactivity of either species. More likely it was due to a combination of the sterically hindered nature of the nucleophile, coupled with further steric clashing, that would be encountered on approach to the small, rigid 4-membered ring of the benzocyclobutenone.

3.2.6 Summary and Conclusions

In what was a pleasing result, palladium-catalysed hydrostannylation of acetylene **3.26** gave the desired stannane, with the correct regiochemistry, in excellent yield. Unfortunately, all attempts at addition of the lithiospecies, derived from stannane **3.39**, to the benzocyclobutenone **2.12** proved fruitless. This prompted investigation of a less sterically demanding stannane **3.45**. Again, no reaction could be induced between the derived lithiospecies and the benzocyclobutenone. Accordingly, investigation into increasing the reactivity of benzocyclobutenone **2.12** was pursued. The chromium complex of 6-methoxybenzocyclobutenone was prepared, but again no reaction could be induced with either lithiospecies. Following this, it was shown that the lithiospecies derived from stannane **3.39** readily reacts with *m*-methoxybenzaldehyde. As seen in Chapter 2, other lithiospecies readily react with benzocyclobutenone **2.12**, therefore the combination of a hindered lithiospecies with a benzocyclobutenone is not compatible for the ensuing bond forming reaction.

It is concluded that the 7-3' biaryl bond of the naphthylisoquinoline alkaloids cannot easily be formed by the aforementioned chemistry. Many approaches were explored, but unfortunately few of the biaryl bond forming reactions were successful enough to warrant further investigation.

The mitigating factor is the hindered nature of both the resulting bond and of the intermediates involved.

Chapter Four

The Enantioselective Total Synthesis of Ancistrocladidine

4.1 Introduction

4.1.1 Biaryl Bond Formation Under Palladium-catalysis

Due to the lack of success of forming a 7-3' biaryl bond by functionalisation of a benzocyclobutenone, or related intermediates, an alternative approach needs to be developed. One such approach involves the assembly of the naphthalene moiety prior to biaryl bond formation.

In previous syntheses of naphthylisoquinoline alkaloids, direct coupling of the appropriate naphthalene and isoquinoline moieties, under palladium catalysis, has proved to be a rewarding approach.³⁷ Disconnection of ancistrocladidine, with this approach in mind, requires the functionalised naphthalene and isoquinoline building blocks shown below (**Figure 4.1**).

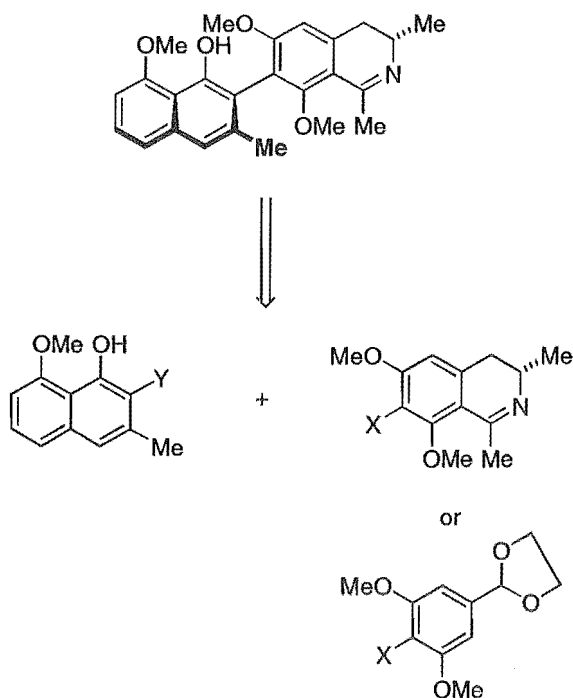


Figure 4.1 Disconnection of ancistrocladidine for a biaryl coupling.

Numerous palladium-catalysed biaryl cross-couplings have been achieved, with the Negishi, Stille, and Suzuki couplings all being utilised in the synthesis of biaryls possessing one, two, or three *ortho*-substituents (Figure 4.2).¹⁰⁵

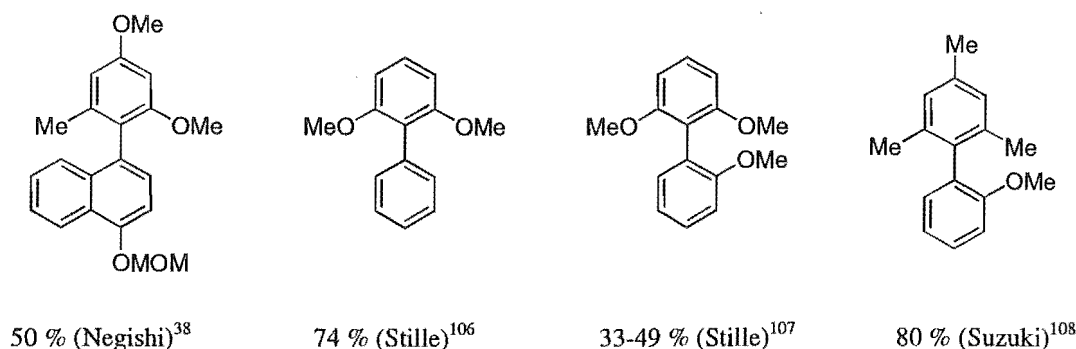
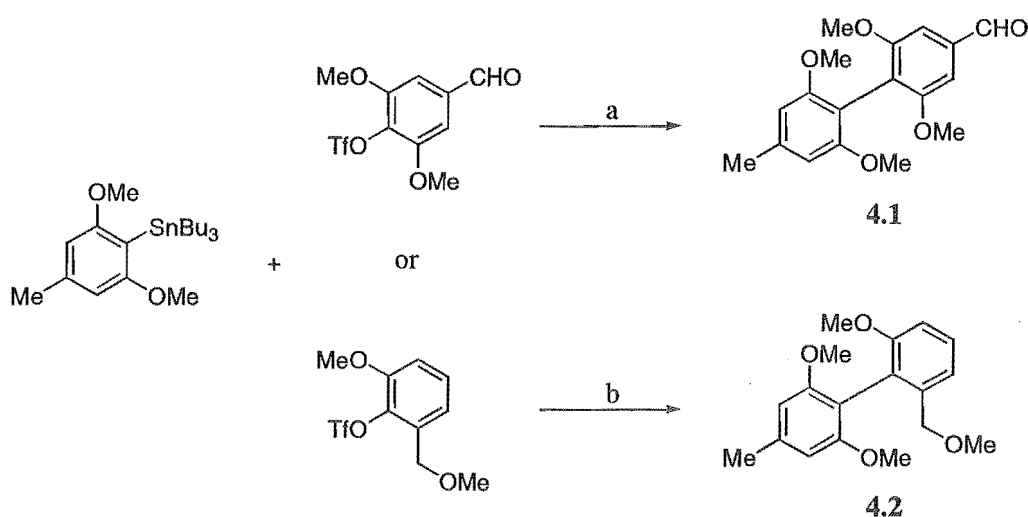


Figure 4.2 Examples of some sterically hindered biaryls prepared by palladium couplings.

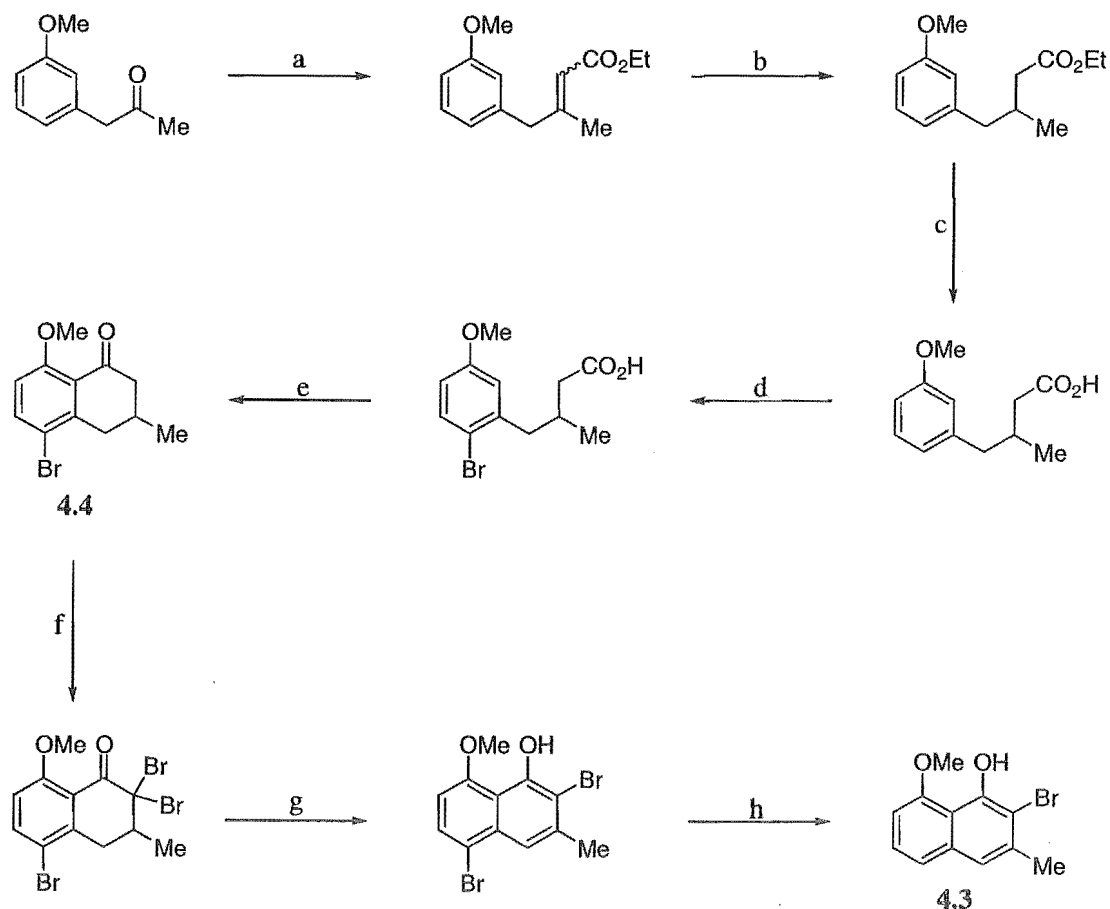
A common trend in such reactions is a lowering in the yield of coupled product upon an increase in the steric bulk surrounding the resulting biaryl bond. For this reason there are few examples of couplings resulting in products which contain four *ortho*-substituents. Saá and Martorell, in their work on palladium-catalysed cross-coupling in the synthesis of biaryls, isolated two 2,2',6,6'-tetrasubstituted biaryls **4.1** and **4.2**, albeit in low yield from complex reaction mixtures (Figure 4.3).¹⁰⁷



Reagents and yields: (a) 10-20 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, LiCl, $\text{P}(o\text{-MePh})_3$, CuBr, DMF, reflux, 25 %; (b) 10-20 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, LiCl, PPh_3 , CuBr, DMF, reflux, 26 %.

Figure 4.3 Synthesis of some biaryls containing four *ortho*-substituents.

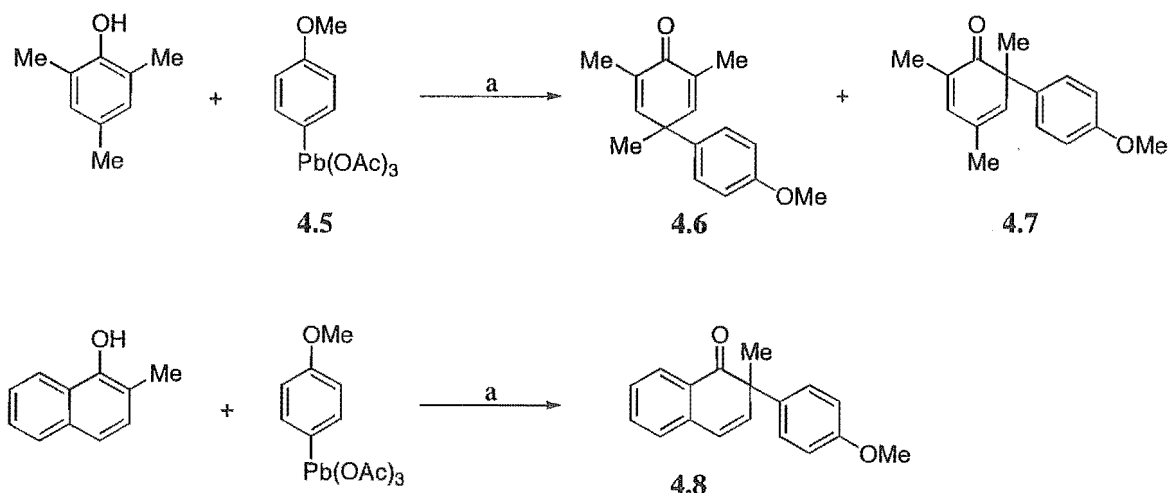
It is evident that formation of a biaryl bond counting four *ortho*-substituents, as present in ancistrocladidine, by palladium-catalysed cross-coupling would most likely be a low yielding process. In addition, synthesis of an appropriate naphthalene precursor is not a trivial process. For example, a suitably functionalised precursor has been prepared by Nishiyama and Kameoka.¹⁰⁹ Naphthol **4.3** was prepared *via* an eight-step sequence, in 7.5 % overall yield, from (3-methoxyphenyl)-2-propanone (**Scheme 4.1**). Although useful, the sequence required many purification steps and included a poor-yielding bromination of tetralone **4.4** (23 %). For these reasons, an alternative biaryl coupling methodology for the formation of a 7-3' biaryl bond was sought.



Scheme 4.1 Reagents and yields: (a) $\text{Ph}_3\text{PCHCO}_2\text{Et}$, 140°C , 90 %; (b) H_2 , Raney Ni, EtOH, r.t., 83 %; (c) KOH, EtOH, reflux, 90 %; (d) Br_2 , CHCl_3 , 0°C , 90 %; (e) PCl_5 , SnCl_4 , benzene, 5°C , 67 %; (f) Br_2 , CHCl_3 , 5°C , 23 %; (g) morpholine, reflux, 80 %; (h) H_2 , Raney Ni, THF/EtOH, r.t., 100 %.

4.1.2 Biaryl Bond Formation Using the Pinhey Reaction

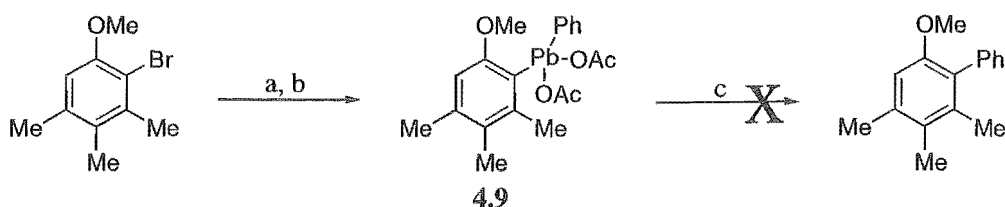
The arylation of phenols with aryllead tricarboxylates is a reaction that is known to proceed on hindered substrates in an efficient manner. This type of coupling was originally reported by Pinhey *et al.*¹¹⁰ It was found that reaction of mesitol with aryllead triacetate **4.5** and equimolar amounts of pyridine in chloroform gave the cyclohexadienones **4.6** and **4.7**, in 95 % yield, in a ratio of 75:20 in favour of the *ortho*-substituted product. A similar reaction conducted on 2-methyl-1-naphthol resulted in formation of naphthalenone **4.8** in 56 % yield (Figure 4.4). A variety of *ortho*-substituted phenols were examined and the key observation was the marked preference for *ortho*-arylation in all cases.



Reagents and yields: (a) Pyridine, CHCl_3 , 95 % for **4.6** and **4.7**, 56 % for **4.8**.

Figure 4.4 Examples of Pinhey's initial work on the reaction of aryllead tricarboxylates with phenols.

At the time Pinhey *et al* were unable to come to any firm conclusions regarding a mechanism for *ortho*-arylation. However, they did suggest that an aryloxylead intermediate may play a key role. In later studies they ruled out the existence of a diaryllead intermediate, such as **4.9**, which failed to undergo a coupling reaction, even under forcing conditions (Scheme 4.2).¹¹¹



Scheme 4.2 Reagents and yields: (a) *n*-BuLi, THF, -78°C , $\text{B}(\text{O}^i\text{Pr})_3$, H_2O , 72 %; (b) $\text{PhPb}(\text{OAc})_3$, CHCl_3 , r.t., 80 %; (c) pyridine, CHCl_3 , 60°C , no reaction.

Barton's group, using their experience with arylbismuth compounds, also studied this *ortho*-arylation reaction with a view to gaining further insight into the proposed mechanism of *ortho*-arylation (Figure 4.5).¹¹² 3,5-Di-*t*-butylphenol was chosen as a coupling partner for the lead reagent. In view of steric constraints it was believed that the formation of arylated products would be improbable, but it was hoped that aryloxylead intermediate **4.10** could be detected by ^1H NMR spectroscopy, thus lending evidence to the proposed mechanism for *ortho*-arylation.

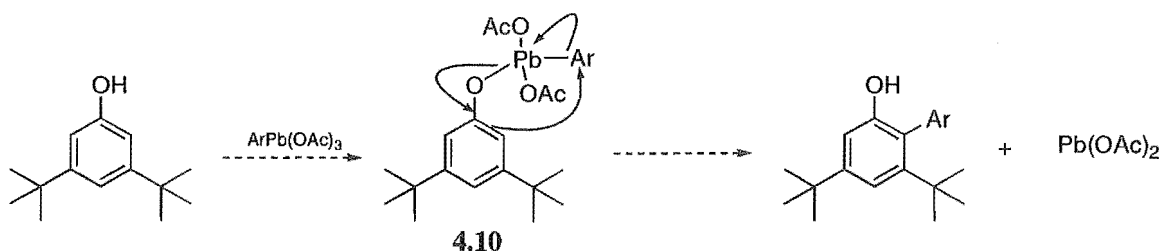
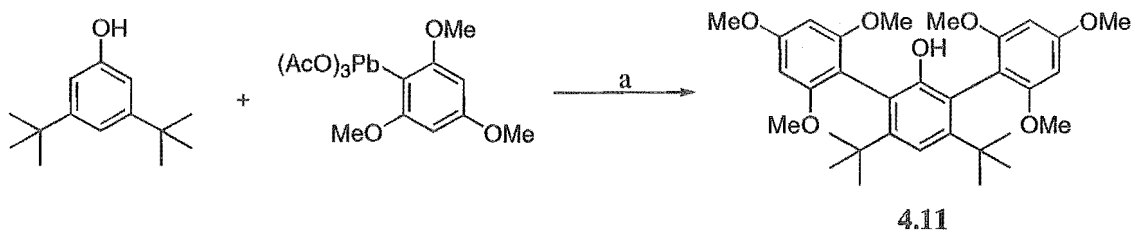


Figure 4.5 The proposed mechanism for *ortho*-arylation.

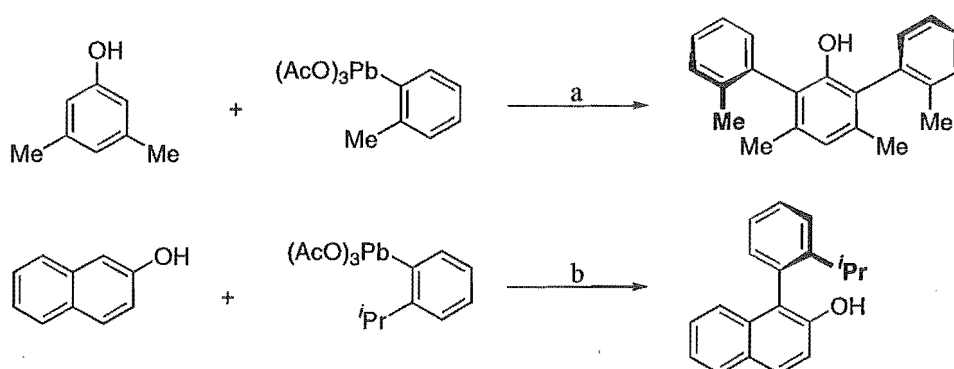
Much to their surprise no intermediate aryloxylead intermediate was detected, but arylation products were shown to be present. Optimisation of the reaction gave the diarylated product **4.11** in an astonishing 87 % yield (Figure 4.6).



Reagents and yield: (a) pyridine, CHCl_3 , r.t., 87 %.

Figure 4.6 *Ortho*-arylation of a sterically hindered phenol.

More recently, Yamamoto *et al* extended this *ortho*-arylation methodology even further to allow asymmetric coupling.¹¹³ Addition of brucine, a chiral base, allowed a range of optically enriched aryl compounds to be prepared as exemplified below (Figure 4.7). The reaction gave high diastereoselectivity, along with moderate to good enantioselectivity.



Reagents and yields: (a) *n*-BuLi, brucine, 4Å sieves, -20 °C, 99 %, 99 % de, 49 % ee; (b) *n*-BuLi, brucine, 4Å sieves, -40 °C, 86 %, 77 % ee.

Figure 4.7 Asymmetric coupling of phenols with aryllead tricarboxylates.

The stereoselectivity was explained using the model depicted below, whereby brucine ligates to the lead and influences the transition state geometry such that the (*M*)-atropisomer is formed preferentially in all cases (Figure 4.8).

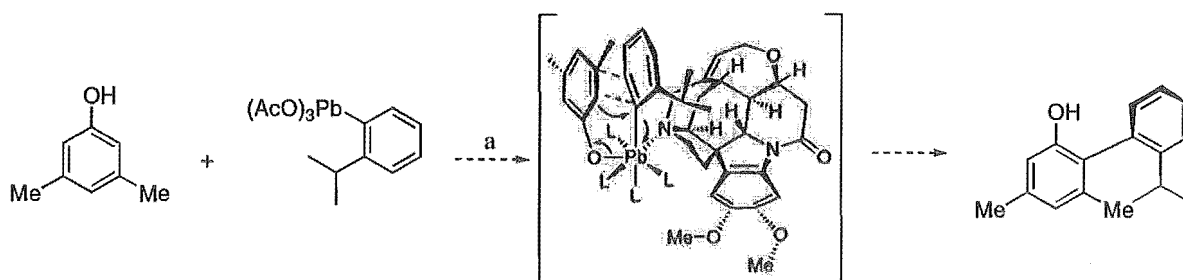


Figure 4.8 A possible transition state to account for the observed asymmetric induction.

This *ortho*-arylation chemistry has far-reaching implications with regards to a synthetic approach to a 7-3' naphthylisoquinoline alkaloid. The possibility exists for direct functionalisation of naphthol 2.58, which would circumvent the need for preparation of a difficult-to-access functionalised naphthalene precursor such as 4.3 (Scheme 4.1). Along with this, the

stereoselective version of this reaction could be exploited to allow a convergent, atropisomeric-selective total synthesis of a 7-3' naphthylisoquinoline alkaloid. However, a reaction such as this would require coupling of the entire heterocyclic moiety as a result of the symmetrical nature of aryllead tricarboxylate **4.12** (Figure 4.9). With this in mind synthesis of an appropriately functionalised dihydroisoquinoline was investigated.

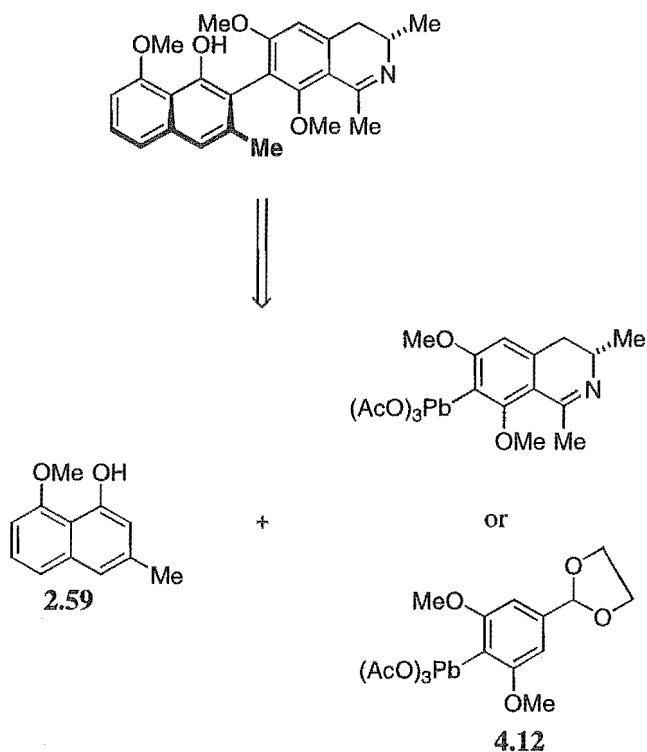


Figure 4.9 Disconnection of ancistrocladidine for a Pb-mediated biaryl coupling.

4.2 Synthesis of Functionalised Heterocyclic Building Blocks

4.2.1 Preparation of a Racemic Heterocyclic Moiety

With most previous syntheses of isoquinoline building blocks, the desired functionality for biaryl coupling is normally introduced at a late stage of the synthesis.¹¹⁴ But as shown in Chapter 3, it is difficult to introduce functionality between the methoxy groups of a dihydro- or tetrahydroisoquinoline. Accordingly, functionality must be introduced at an earlier stage,

followed by elaboration of the isoquinoline functionality to give the functionalised heterocycles **4.13** and **4.14**. This could be achieved by starting with aldehyde **3.6** (Figure 4.10).

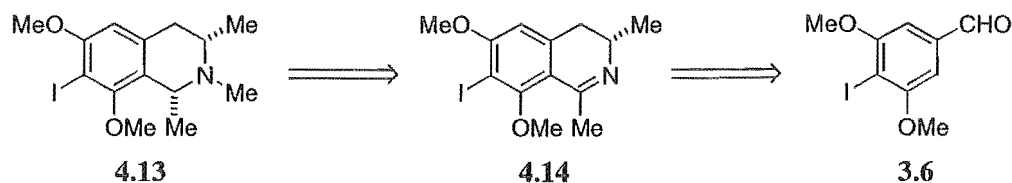
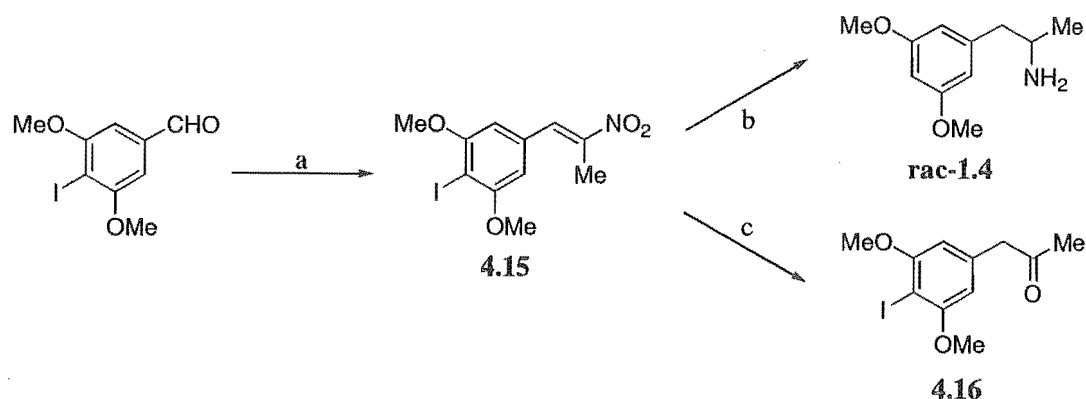


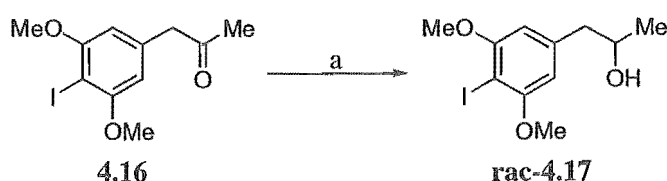
Figure 4.10 Aldehyde **3.6**, a precursor to functionalised heterocycles **4.13** and **4.14**.

It was decided to investigate a short non-stereoselective synthesis of dihydroisoquinoline **4.14** to determine the relative merit of carrying the iodide functionality through such a sequence. This began with a Henry reaction on aldehyde **3.6**, which gave the desired nitrostyrene **4.15** in 70 % yield. Not unexpectedly, reduction of nitrostyrene **4.15** with lithium aluminium hydride in THF effected deiodination, as well as the desired reduction, to yield amine **rac-1.4**. Accordingly, an alternative procedure was pursued. Reduction of the nitrostyrene with iron powder in refluxing acetic acid proceeded smoothly to give ketone **4.16** in 94 % yield (Scheme 4.3).



Scheme 4.3 Reagents and yields: (a) EtNO_2 , NH_4OAc , HOAc , reflux, 70 %; (b) LiAlH_4 , THF, reflux; (c) Fe powder, HOAc , reflux, 94 %.

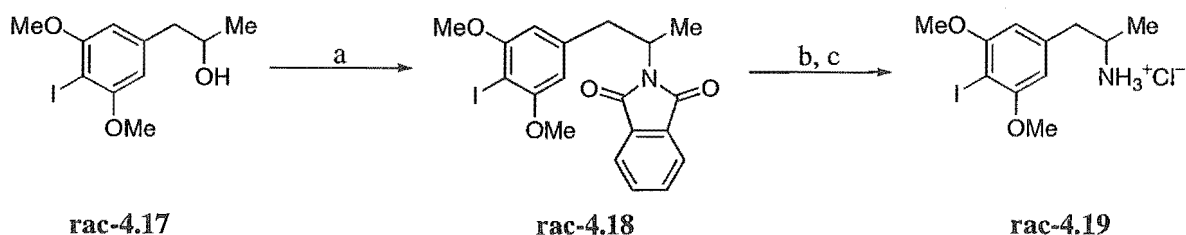
Introduction of the nitrogen functionality *via* ketone **4.16** was achieved by a Mitsunobu reaction on the derived alcohol. The requisite alcohol **rac-4.17** was prepared in 95 % yield by reduction of ketone **4.16** with DIBAL in dichloromethane (Figure 4.11).



Reagents and yield: (a) DIBAL, CH_2Cl_2 , 0°C , 95 %.

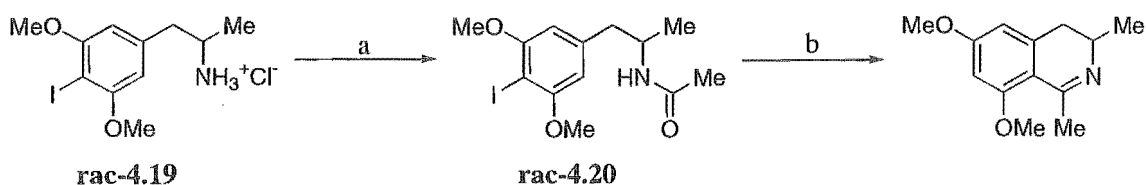
Figure 4.11 Reduction of ketone **4.16**.

Phthalimide was chosen as the source of *N*-functionality for the ensuing Mitsunobu reaction as it is easily handled and can be readily deprotected to liberate a free amine.¹¹⁵ Reaction of alcohol **rac-4.17** with triphenylphosphine, phthalimide, and diethyl azodicarboxylate, in THF gave imide **rac-4.18** in 81 % yield after chromatography. Deprotection was readily accomplished by refluxing the imide in an ethanolic solution of aqueous methylamine to give the amine, which was isolated in 91 % yield as its hydrochloride salt **rac-4.19** (Scheme 4.4).



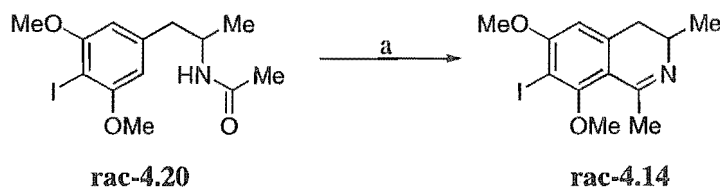
Scheme 4.4 Reagents and yields: (a) Phthalimide, PPh_3 , DEAD, THF, 0°C to r.t., 81 %; (b) MeNH_2 , $\text{H}_2\text{O}/\text{EtOH}$, reflux; (c) HCl (g), ether, 0°C , 91 % for 2 steps.

With ready access to the amine achieved, attention could be focused upon annelation of the remainder of the heterocyclic moiety. The standard protocol for this is acetylation, followed by Bischler-Napieralski cyclisation.¹⁰ Hydrochloride **rac-4.19** was smoothly acetylated using acetyl chloride and triethylamine in dichloromethane to give acetamide **rac-4.20** in 96 % yield. However, the ensuing Bischler-Napieralski cyclisation was problematic. Exposure of the acetamide to the standard cyclisation conditions of phosphorus oxychloride in acetonitrile at reflux, resulted in varying degrees of deiodination (Scheme 4.5).



Scheme 4.5 Reagents and yield: (a) CH_3COCl , NEt_3 , CH_2Cl_2 , 0 °C to r.t., 96 %; (b) POCl_3 , CH_3CN , reflux.

It was postulated that acid generated *in situ* was causing the ensuing deiodination. Lipshutz and Keith, in their synthesis of a tetrahydroisoquinoline building block, conducted a successful Bischler-Napieralski cyclisation in the presence of a TBS ether.¹⁴ This was achieved by addition of 2,4,6-collidine to the reaction, presumably to act as an acid scavenger. Pleasingly, it was found that cyclisation of the acetamide **rac 4.20** in the presence of 1 equivalent of 2,4,6-collidine resulted in a much cleaner reaction, giving the desired iododihydroisoquinoline **rac-4.14** in 89 % yield, after purification (**Figure 4.12**).



Reagents and yield: (a) POCl_3 , 2,4,6-collidine, CH_3CN , reflux, 89 %.

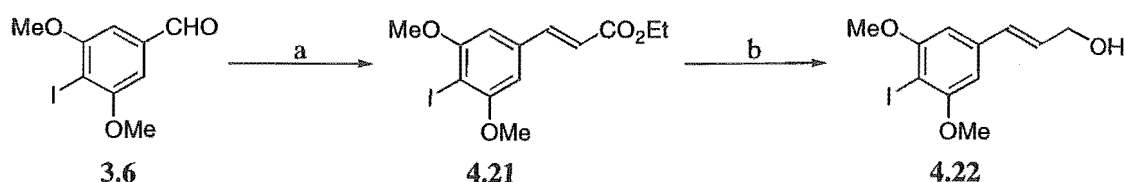
Figure 4.12 Successful cyclisation of the acetamide.

Armed with the knowledge that the iodide moiety could be carried through such a synthesis, efforts were now focused upon generating an enantioselective synthesis of **4.14**.

4.2.2 Preparation of Chiral Heterocyclic Building Blocks

As discussed in Chapter 1, there are a number of methods for the preparation of optically active tetrahydro- or dihydroisoquinoline building blocks. Either the asymmetric dihydroxylation or asymmetric epoxidation procedures could be useful in terms of their reliability, mild reaction conditions, and relative stability of the intermediates involved. The methodology chosen for introduction of chirality in this work was Sharpless asymmetric epoxidation as it would

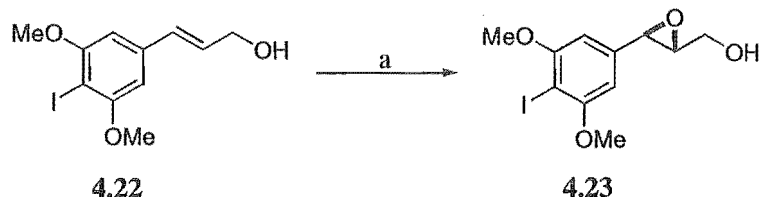
conveniently intersect with an intermediate in the previously developed non-stereoselective synthesis. The epoxidation procedure was pioneered for use in naphthylisoquinoline alkaloid synthesis by Rao *et al.* as outlined earlier in **Scheme 1.5**.¹⁵ The required functionality for a successful Sharpless asymmetric epoxidation is an allylic alcohol, which can be readily introduced by a two-step procedure. Accordingly, deprotonation of triethylphosphonoacetate with sodium hydride in benzene, followed by addition of aldehyde **3.6** gave ester **4.21** in quantitative yield. Reduction of the ester with DIBAL gave allylic alcohol **4.22** in 80 % yield (**Scheme 4.6**).



Scheme 4.6 Reagents and yields: (a) $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, NaH, benzene, 0 °C to r.t., 100 %; (b) DIBAL, CH_2Cl_2 , 0 °C, 80 %.

With the allylic alcohol in hand, attention was now turned to an enantioselective epoxidation of this compound. The Sharpless epoxidation procedure relies upon the formation of a titanium complex whose ligands include a tartrate ester (the source of chirality), *t*-BuOOH (the epoxidising agent), and the allylic alcohol. As a result of the geometry of this complex, which depends on the chirality of the chosen tartrate, only one face of the allylic alcohol is presented to the bound epoxidising agent. Therefore, upon delivery of the epoxide oxygen, one enantiomer is produced in preference to the other. Before embarking on the epoxidation procedure the relative disconnections had to be made in order to deduce the stereochemistry of the desired epoxide and therefore, of the required tartrate ligand. It follows that (*S*)-configured dihydroisoquinoline **4.14** would require an (*S*)-configured amine, which in turn would be derived from Mitsunobu inversion of an (*R*)-configured alcohol. The stereochemistry of this alcohol results from a (2*S*, 3*R*)-configured epoxide. The choice of tartrate ligand, which dictates the stereochemical outcome of the epoxidation, is readily achieved using the model developed by Sharpless.¹¹⁶ When the allylic alcohol is correctly positioned on the template, a complex containing *D*-(-)-diisopropyltartrate delivers oxygen to the top face, whereas *L*-(+)-diisopropyltartrate delivers oxygen to the bottom face. Thus, for the desired (2*S*, 3*R*)-epoxide, *D*-(-)-diisopropyltartrate will give the correct facial selectivity. Accordingly, treatment of allylic alcohol **4.22** under standard

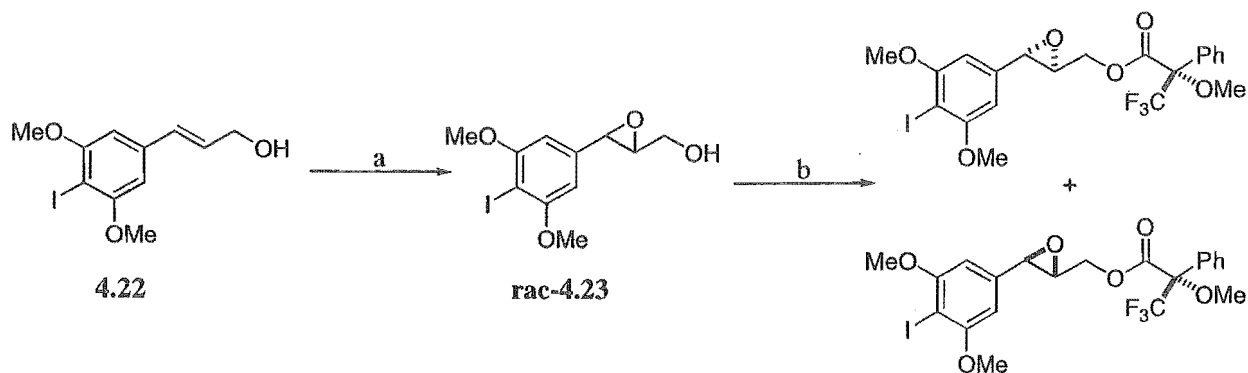
Sharpless epoxidation conditions¹¹⁷ gave epoxide **4.23** in 84 % yield after chromatography (Figure 4.13).



Reagents and yield: (a) $\text{Ti}(\text{OiPr})_4$, $t\text{-BuOOH}$, (*D*)-(-)-diisopropyltartrate, 4Å sieves, CH_2Cl_2 , -20°C , 84 %, 90 % ee.

Figure 4.13 Sharpless asymmetric epoxidation of allylic alcohol **4.22**.

In order to determine the efficiency of asymmetric induction, the method described by Mosher was chosen.¹¹⁸ This involves reaction of an alcohol with an optically pure acid chloride. The resulting ratio of diastereoisomers is determined by integration of the appropriate peaks in the ^1H NMR spectrum, from which is derived the enantiomeric excess (ee) for the epoxidation reaction. In order to allow integration of the correct peaks a sample of the racemic epoxide was prepared. This was achieved by reaction of allylic alcohol **4.22** with catalytic vanadyl acetylacetonate and $t\text{-BuOOH}$ in dichloromethane¹¹⁹, which gave epoxide **rac-4.23** in 91 % yield after chromatography. Preparation of the Mosher ester of **rac-4.23** was carried out by treatment of a solution of the epoxide **rac-4.23**, DMAP, and triethylamine in dichloromethane with a solution of MTPA-Cl in dichloromethane (Scheme 4.7). The reaction was monitored by TLC to ensure complete consumption of starting material, which is important so as to avoid kinetic resolution as this can affect the calculated ee.



Scheme 4.7 Reagents and yield: (a) $\text{VO}(\text{acac})_2$, $t\text{-BuOOH}$, CH_2Cl_2 , r.t., 91 %; (b) (*S*)-MTPA-Cl, NEt_3 , DMAP, CH_2Cl_2 , r.t.

Analysis of the ^1H NMR spectrum of the Mosher esters derived from **rac-4.23** revealed the expected 1:1 mixture of diastereoisomers. Following this, the procedure was repeated on epoxide **4.23** obtained from the asymmetric epoxidation. The resulting 95:5 mixture of diastereoisomers equated to 90 % ee for the original epoxidation reaction. Pleasingly, recrystallisation from toluene/petroleum ether gave epoxide **4.23** in 73 % yield and >95 % ee. Shown below are representative ^1H NMR spectra for the Mosher esters derived from the racemic and optically enriched epoxides respectively (Figure 4.14).

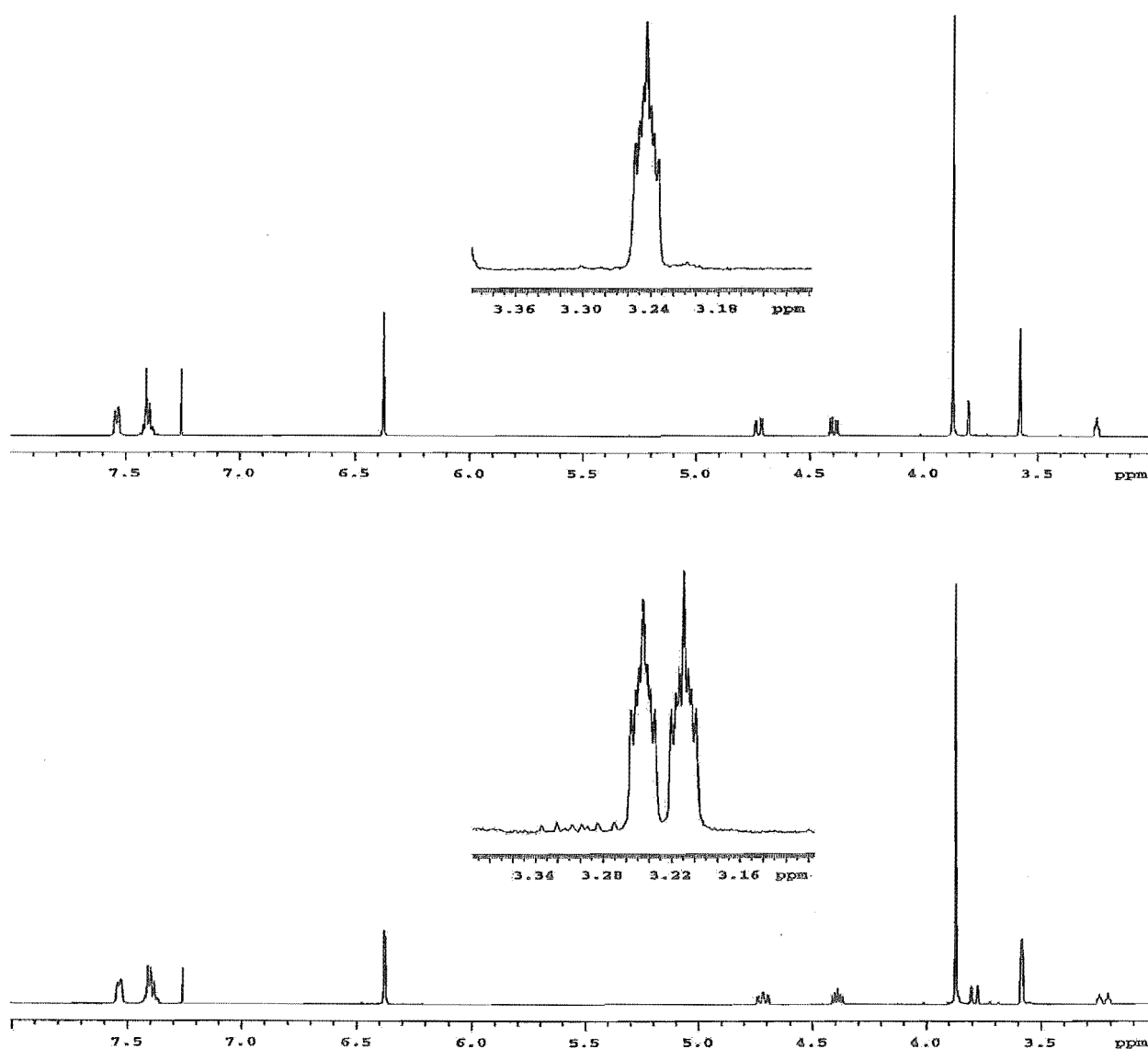


Figure 4.14 500 MHz ^1H NMR spectra of the Mosher esters derived from epoxides **4.22**.

With the stereochemistry now set, manipulation of the functional groups was required in order to allow introduction of nitrogen functionality. Firstly, an appropriate leaving group needed to be introduced, which would allow reductive ring opening of the epoxide. Chong studied a variety of leaving groups and reducing agents for the regioselective ring opening of 2,3-epoxyalcohol derivatives.¹²⁰ It was concluded that if the leaving group was reduced before the epoxide, then this would lead to low regioselectivity in the subsequent epoxide opening. Alternatively, if epoxide opening occurs first, followed by intramolecular epoxide formation and subsequent regioselective reduction, this would lead predominantly to the desired alcohol (**Figure 4.15**).

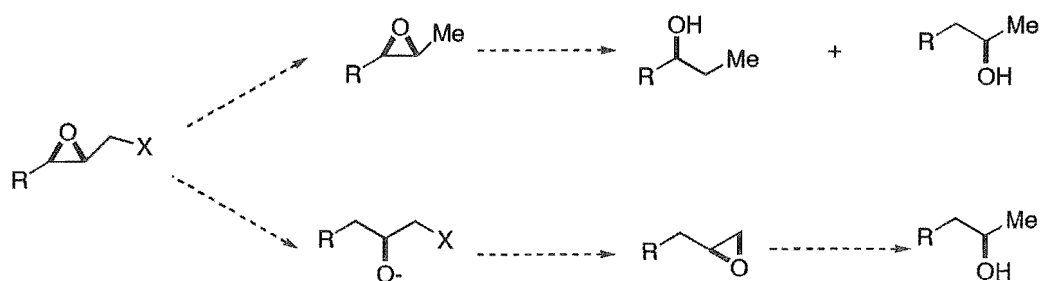
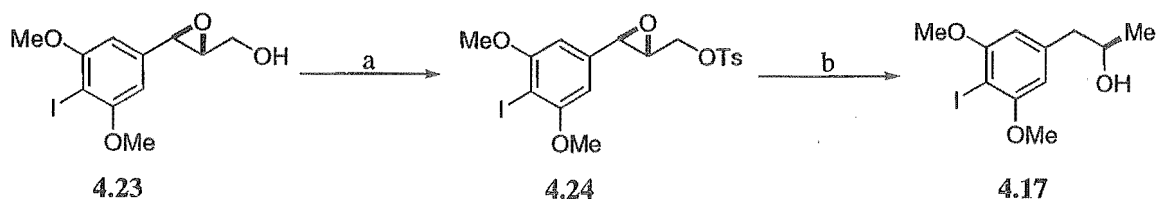


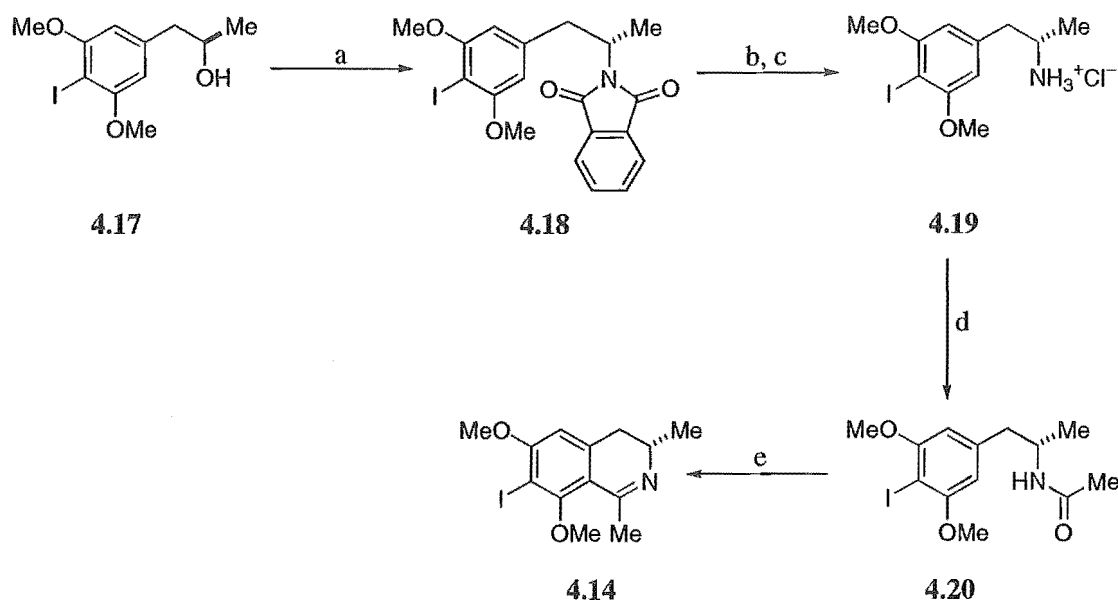
Figure 4.15 Mechanistic considerations for the reductive ring opening of epoxytosylates.

Chong found that the DIBAL reduction of epoxytosylates was the best combination of reactants. The reaction was also shown to proceed with complete stereochemical integrity making it a powerful tool, in combination with asymmetric epoxidation, for the synthesis of optically pure 2-alkanols. Accordingly, tosylate **4.24** was readily prepared from epoxyalcohol **4.23** in 95 % yield. Subsequent reduction with DIBAL in dichloromethane gave alcohol **4.17** in 94 % yield after chromatography (**Scheme 4.8**).



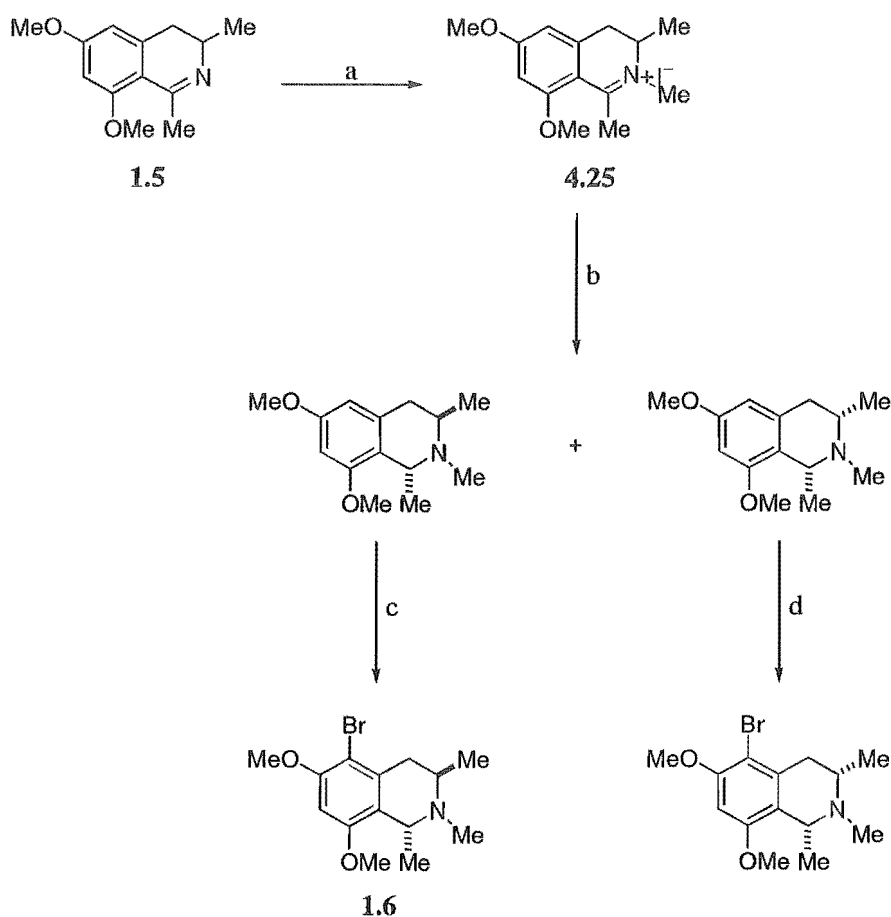
Scheme 4.8 Reagents and yields: (a) TsCl, NEt₃, DMAP, CH₂Cl₂, 0 °C, 95 %; (b) DIBAL, CH₂Cl₂, – 20 °C to r.t., 94 %.

At this point the asymmetric synthesis intersected with the previously developed racemic approach. Accordingly, alcohol **4.17** was smoothly carried through the remainder of the sequence to give chiral dihydroisoquinoline building block **4.14** (Scheme 4.9).



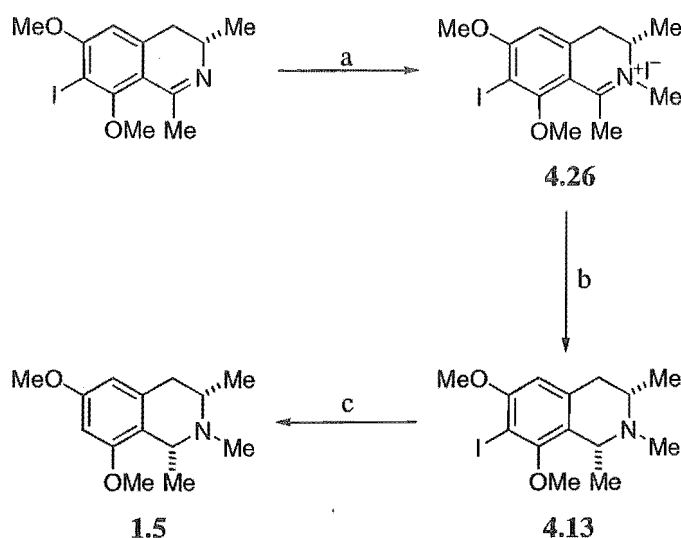
Scheme 4.9 Reagents and yields: (a) Phthalimide, PPh_3 , DEAD, THF, 0°C to r.t., 81 %; (b) MeNH_2 , $\text{H}_2\text{O}/\text{EtOH}$, reflux; (c) HCl (g), ether, 0°C , 91 % for 2 steps; (d) CH_3COCl , NEt_3 , CH_2Cl_2 , 0°C to r.t., 96 %; (e) POCl_3 , 2,4,6-collidine, CH_3CN , reflux, 89 %.

The other 7-3' linked naphthylisoquinoline alkaloid, ancistrocladidine **1.100**, contains a tetrahydroisoquinoline moiety and it was decided to prepare this moiety in anticipation of a total synthesis. It is well documented that reduction of 3,4-dihydroisoquinolines with sodium borohydride in methanol gives *cis*-configured tetrahydroisoquinolines.¹⁰ These can be converted into their *N*-methyl derivatives by preparation of the carbamate, followed by lithium aluminium hydride reduction.^{29d} However, it has already been shown that the iodide functionality is not compatible with such a reducing agent, therefore an alternative method was sought. Rizzacasa and Sargent have shown that *N*-methylation of dihydroisoquinoline **1.5** can be achieved, but reduction of the resulting tetrahydroisoquinolinium salt **4.25**, with sodium borohydride, gave a 2:1 mixture of tetrahydroisoquinolines in favour of the *trans*-isomer (Scheme 4.10). Separation and subsequent bromination of the diastereoisomers was readily achieved and the stereochemistry of **1.6** was confirmed by single crystal X-ray structural determination.¹¹



Scheme 4.10 Reagents and yields: (a) MeI, EtOAc, r.t., 84 %; (b) NaBH₄, EtOH, r.t., *trans* 59 %, *cis* 29 %; (c) Br₂, CH₂Cl₂, 0 °C, 68 %; (d) Br₂, CH₂Cl₂, 0 °C, 65 %.

As ancistrocladine contains a *cis* arrangement of the methyl groups, an alternative reducing agent was required. There was evidence to suggest that reduction of isoquinolinium salts with the bulkier diisobutylaluminium hydride should give the desired *cis*-selectivity.¹²¹ Accordingly, *N*-methyldihydroisoquinoline 4.26 was readily prepared by treating a solution of the dihydroisoquinoline in acetone with iodomethane. The so-obtained salt was reduced with DIBAL in dichloromethane at −78 °C. This resulted in a 9:1 ratio of diastereoisomers, as observed by ¹H NMR spectroscopy. The major diastereoisomer 4.13 was obtained in 85 % yield upon chromatographic separation on alumina - the minor isomer did not elute (Scheme 4.11). The relative configuration was confirmed by deiodination using *t*-BuLi then H₂O, which gave the known tetrahydroisoquinoline *cis*-1.5 reported by Sargent and Rizzacasa.¹¹



Scheme 4.11 Reagents and yield: (a) MeI, acetone, r.t.; (b) DIBAL, CH₂Cl₂, -78 °C to r.t., 85 % for 2 steps; (c) *t*-BuLi/H₂O, THF, -78 °C.

The observed stereoselectivity for the reduction of the isoquinoline could be explained in terms of the bulky reducing agent delivering a hydride from the opposite face with respect to the methyl group at 3-position. This is in contrast to the reduction of 3,4-dihydroisoquinolines using a combination of LiAlH₄/AlMe₃, which gives *trans*-selectivity as a result of precoordination of the bulky AlMe₃ molecule to the lone pair on nitrogen. This bulky group would tend to sit away from the methyl group at the 3-position blocking this face, thus forcing hydride delivery from the same side as the methyl group.¹² Following the successful development of a synthesis of chiral heterocyclic building blocks, investigations into conversion of these compounds into the desired aryllead species could be pursued.

4.2.3 Investigations into the Synthesis of Chiral Aryllead Precursors

Organolead compounds may be prepared by two routes, either by direct plumbation or by transmetalation.¹²² The latter method is the more general route as it exhibits a greater tolerance of functionality. This metal-metal exchange route is normally achieved using either a tin¹²³ or boron¹²⁴ species in the presence of catalytic amounts of mercuric (II) salts. Tin-lead exchange has proven to be the method of choice in many cases due to the ease of purification of the resulting organolead compounds (Figure 4.16). The by-product from the exchange reaction is

tributyltin acetate, which is readily removed by washing the product with petroleum ether, leaving the pure organolead compound.

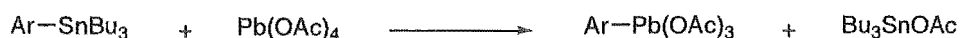
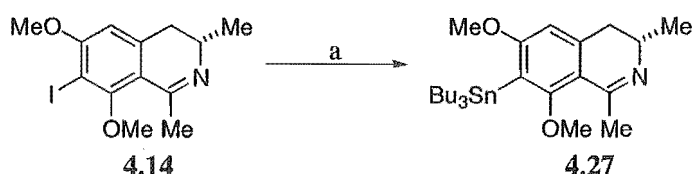


Figure 4.16 General transmetalation of stannanes to produce aryllead tricarboxylates.

It was envisaged that iodide **4.14** would readily undergo halogen/metal exchange with *t*-BuLi, following which quenching with tributyltin chloride would give the stannane, a precursor to the desired aryllead species. Indeed, treatment of the iodide with *t*-BuLi at $-95\text{ }^\circ\text{C}$ in THF, followed by addition of tributyltin chloride gave stannane **4.27** in a pleasing 83 % yield (**Figure 4.17**).



Reagents and yield: (a) *t*-BuLi, THF, $-95\text{ }^\circ\text{C}$, ClSnBu_3 , $-95\text{ }^\circ\text{C}$ to r.t., 83 %.

Figure 4.17 Preparation of stannane **4.27**.

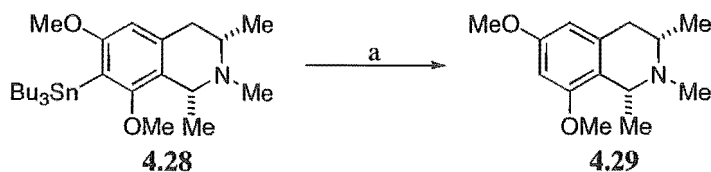
The standard protocol for preparation of aryllead compounds from stannanes is stirring the stannane with stoichiometric quantities of lead tetraacetate and catalytic amounts of mercuric acetate in chloroform at $40\text{ }^\circ\text{C}$.^{123b} Unfortunately, exposure of stannane **4.27** to these conditions resulted in a complex mixture, from which only starting material could be isolated. The reaction was repeated at room temperature and it was noted that upon addition of stannane to a solution of freshly dried lead tetraacetate, red coloration and precipitation of material resulted. The precipitated material appeared to dissolve in water, but no useful information could be gathered from the resulting ^1H NMR spectrum run in D_2O . It was postulated that lead tetraacetate was reacting with the nitrogen on the dihydroisoquinoline. It was decided to investigate the reactivity of the stannane **4.28** derived from iodide **4.13** in the transmetalation reaction. Stannane **4.28** was prepared in 56 % yield from iodide **4.13** by halogen/metal exchange, followed by addition of tributyltin chloride (**Figure 4.18**).



Reagents and yield: (a) *t*-BuLi, THF, $-95\text{ }^{\circ}\text{C}$, ClSnBu_3 , $-95\text{ }^{\circ}\text{C}$ to r.t., 56 %.

Figure 4.18 Preparation of stannane **4.28**.

Stirring a solution of the stannane **4.28**, lead tetraacetate, and mercuric acetate at room temperature gave only recovered starting material and a small amount of demetalated material **4.29**. Repeating the reaction, but at $40\text{ }^{\circ}\text{C}$ resulted in complete demetalation to form **4.29** (Figure 4.19).



Reagents and conditions: (a) $\text{Pb}(\text{OAc})_4$, cat $\text{Hg}(\text{OAc})_2$, CHCl_3 or CH_2Cl_2 .

Figure 4.19 Demetalation of stannane **4.28**.

Barton *et al* observed that arylamine **4.30** was slowly oxidised by aryllead reagent **4.31** and proposed the mechanism depicted in Figure 4.20.¹²⁵ Attack of the electron-rich amine on the electrophilic lead atom could form intermediate **4.32**, which following oxidation and expulsion of an acetate ion would form aryllead(II) amine **4.33**, which undergoes acetolysis to form demetalated species **4.34** and lead(II) acetate.

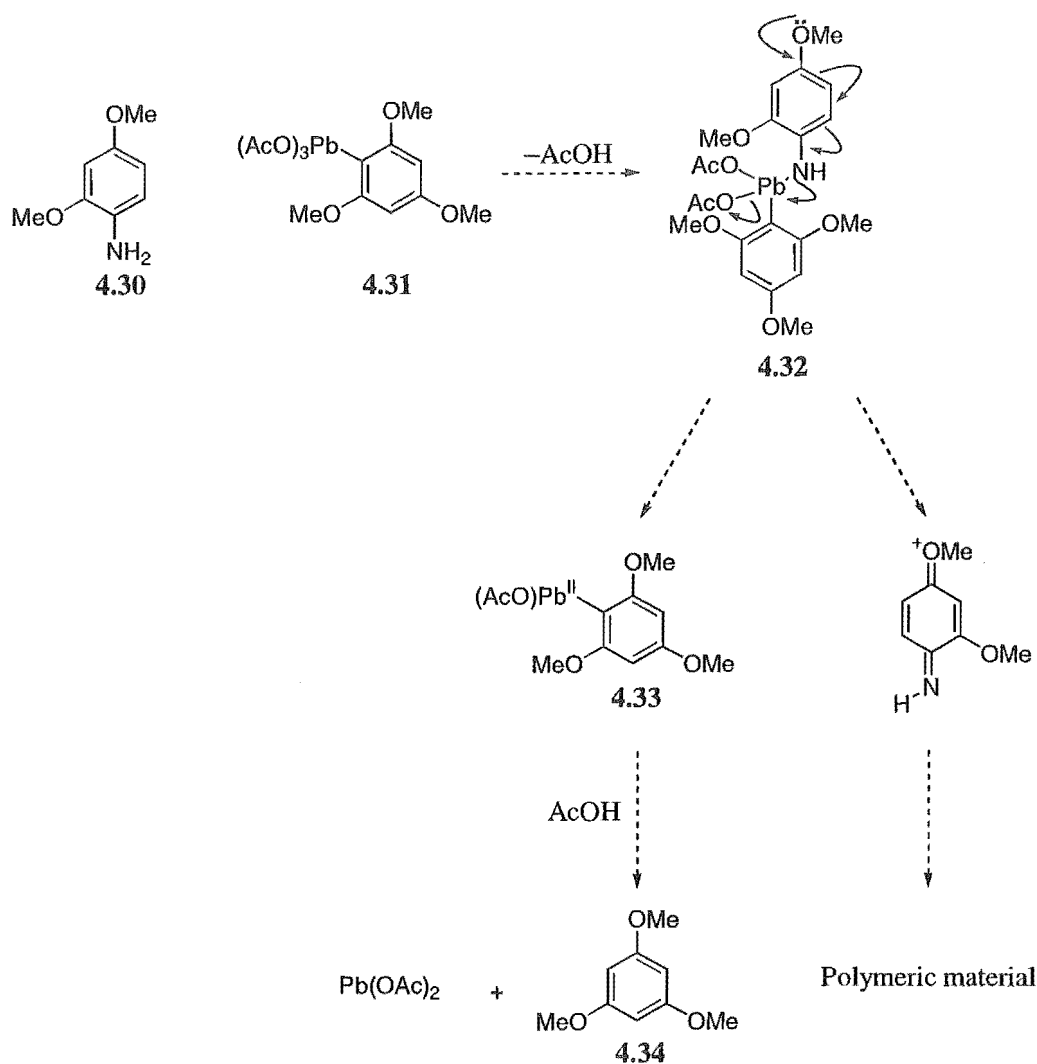
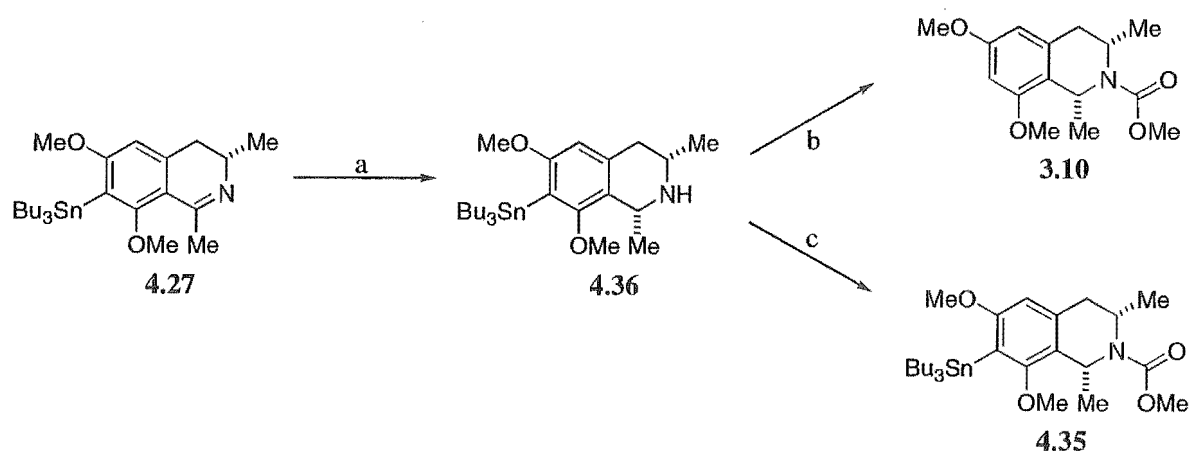


Figure 4.20 Barton *et al.*'s proposed mechanism for demetalation.

A similar demetalation mechanism could be in operation for the tetrahydroisoquinoline aryllead species. Two potential solutions to this problem were considered at this stage. Firstly, *in situ* trapping of the aryllead species with naphthol 2.59, which may be a faster process than the proposed oxidation, or secondly an electron-withdrawing group could be attached to the nitrogen atom of the tetrahydroisoquinoline, thus decreasing the basicity of the lone pair of electrons and hindering the undesired nucleophilic addition to lead.

Unfortunately, conducting the plumbation reaction in the presence of the naphthol 2.59 and pyridine resulted in a complex mixture from which only starting materials and demetalated species could be isolated. Accordingly, the alternative solution was investigated. As the

carbamate group would provide significant withdrawal of electron density from the nitrogen and can be readily converted into an *N*-methyl derivative, carbamate **4.35** was chosen as a potential precursor to an aryllead species. Stannane **4.27** was readily reduced with sodium borohydride in methanol to give amine **4.36** in 96 % yield. Reaction of the amine with methyl chloroformate and sodium bicarbonate in dichloromethane resulted in demetalated carbamate **3.10**, indicating that sodium bicarbonate was not acting as an efficient acid scavenger (Scheme 4.12). Pleasingly, it was found that carbamate **4.35** could be readily prepared in 77 % yield by reacting amine **4.36** with methyl chloroformate in dichloromethane, in the presence of triethylamine. Interestingly the aliphatic CH signals were significantly broadened in the ^1H NMR spectrum of carbamate **4.35**. This may arise from a slowing of the rate of pyramidal inversion at nitrogen by the electron-withdrawing carbamate group.^{126,127}

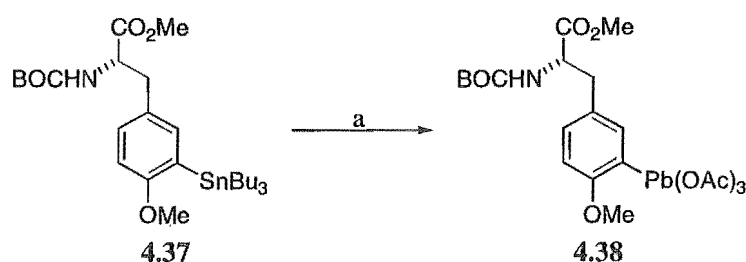


Scheme 4.12 Reagents and yields: (a) NaBH₄, MeOH, r.t., 96 %; (b) ClCO₂Me, NaHCO₃, CH₂Cl₂, r.t.; (c) ClCO₂Me, NEt₃, CH₂Cl₂, r.t., 77 %.

Stirring of stannane **4.35** with lead tetraacetate and mercuric acetate in chloroform at r.t. gave only recovered starting material and a small amount of demetalated material. Conducting the reaction at 40 °C resulted in an increase in the amount of demetalated material.

4.2.4 Summary

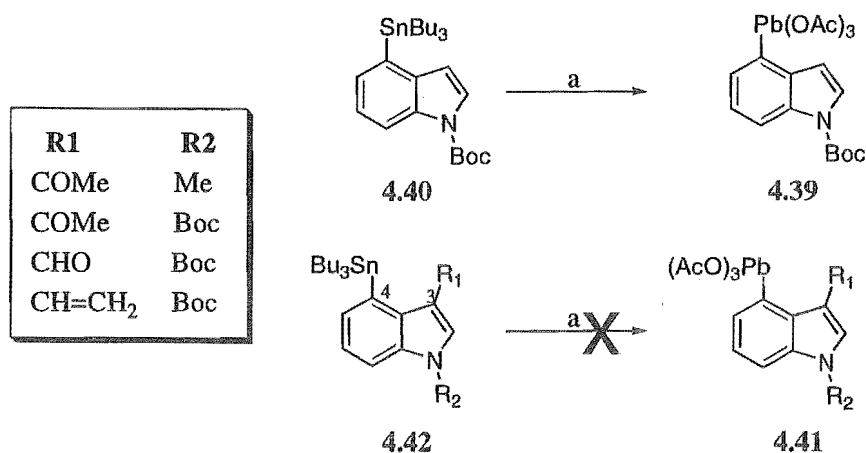
Upon further examination of the literature, it is of note that few nitrogen-containing aryllead compounds are known, presumably as a result of the reactivity of this atom toward lead compounds. However, a recent review by Elliot and Konopelski gave two examples of nitrogen-containing lead species.¹²⁸ The first of these was prepared by Konopelski *et al* in their synthetic studies on Diazonamide A (Figure 4.21).¹²⁹ The tyrosine fragment 4.37 readily underwent tin-lead exchange to give aryllead tricarboxylate 4.38 in 85 % yield.



Reagents and yields: (a) $\text{Pb}(\text{OAc})_4$, cat $\text{Hg}(\text{OAc})_2$, CHCl_3 , 40 °C, 85 %.

Figure 4.21 Successful preparation of a lead compound from a tyrosine derivative.

Following this Konopelski and Deng prepared aryllead 4.39 from stannane 4.40, but interestingly, the corresponding aryllead reagents 4.41 could not be prepared from stannanes 4.42 (Figure 4.22).¹³⁰ It was postulated that steric and/or electronic factors arising from the close proximity of the C4 and C3 substituents were involved.



Reagents and yield: (a) $\text{Pb}(\text{OAc})_4$, cat $\text{Hg}(\text{OAc})_2$, CHCl_3 , 40 °C, 90 %.

Figure 4.22 Konopelski and Deng's studies on nitrogen-containing lead compounds.

The inability of stannanes **4.27**, **4.28**, and **4.35** to form an aryllead species could be due to a number of factors. For instance, an argument based upon steric grounds alone is not supported by the relative ease with which aryllead triacetate **4.31** is formed, whereby the resulting lead moiety is flanked by two methoxy groups. The presence of a nitrogen atom containing a basic lone pair of electrons could be detrimental, as it has been shown that nitrogen-containing species such as pyridine interact strongly with aryllead triacetates in solution.¹¹⁰ A possible steric argument can also be considered when comparing aryllead tricarboxylates **4.43** and **4.31**. A steric clash between the C8 methoxy group and the C1 methyl group could cause a subtle compression of the steric environment between the methoxy groups resulting in an inability to form a lead-species. It is possible to remove the issues associated with the nitrogen atom and those associated with steric crowding by investigating the synthesis of aryllead tricarboxylate **4.12** (Figure 4.23).

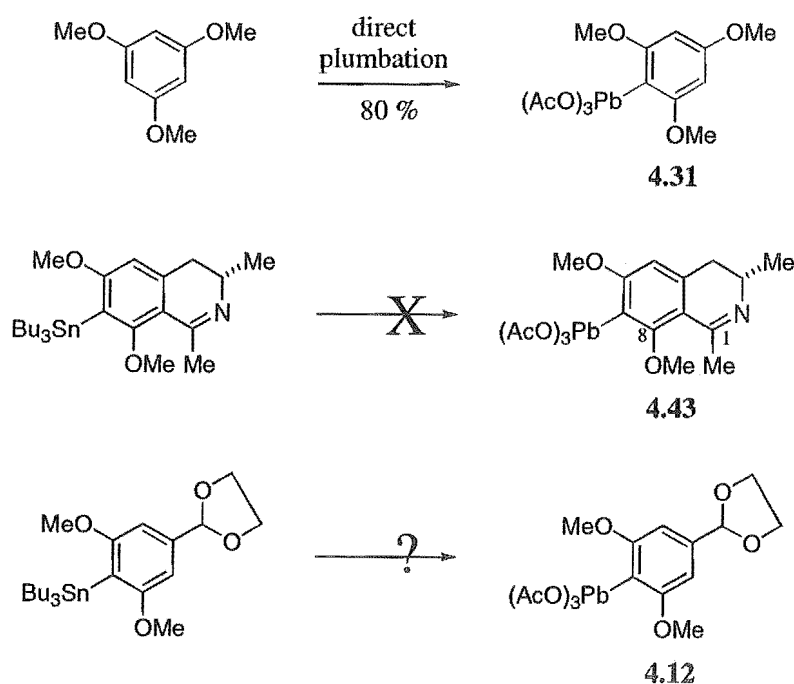


Figure 4.23 A comparison of aryllead tricarboxylates.

4.3 Investigation of a Simpler Aryllead Tricarboxylate

4.3.1 Introduction

An approach that involves assembly of the 3,4-dihydroisoquinoline ring after the formation of the biaryl-bond would offer no control over the stereochemistry of the biaryl bond. Diastereoisomers would be produced as a consequence of the loss of symmetry upon cyclisation, as there are two potential sites at which the ensuing electrophilic aromatic substitution can take place. As a result of restricted rotation about the central biaryl bond, attack at either of these positions would result in the formation of atropisomers. However, provided the dihydroisoquinoline moiety can be assembled in a stereoselective fashion, separation of the resulting diastereoisomers should be possible.

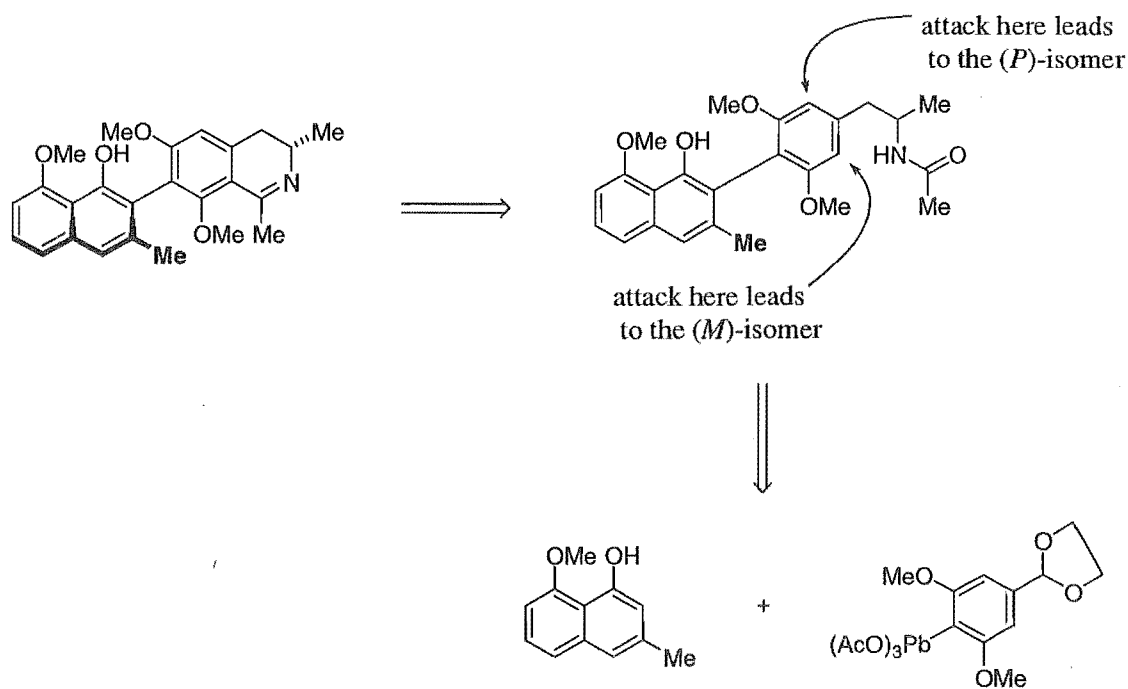
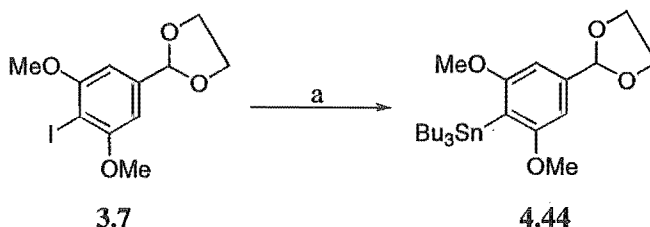


Figure 4.24 An alternative biaryl coupling.

4.3.2 Synthesis of the Aryllead Triacetate

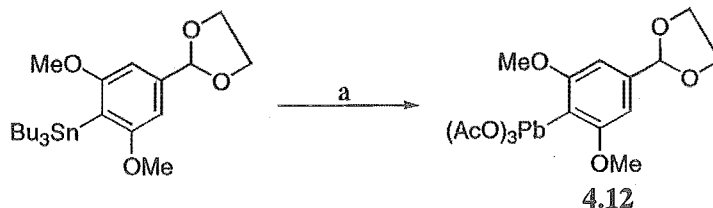
The precursor to aryllead triacetate **4.12** is stannane **4.44**. This was readily prepared by halogen/metal exchange of iodide **3.7** with *t*-BuLi at $-95\text{ }^{\circ}\text{C}$ in THF. Subsequent quenching of the lithiospecies with tributyltin chloride gave stannane **4.42** in 85 % yield (Figure 4.25).



Reagents and yield: (a) *t*-BuLi, THF, $-95\text{ }^{\circ}\text{C}$, ClSnBu_3 , $-95\text{ }^{\circ}\text{C}$ to r.t., 85 %.

Figure 4.25 Preparation of stannane **4.44**.

Exposure of the stannane to standard aryllead forming conditions gave a promising result. Analysis of the ^1H NMR spectrum of the reaction mixture revealed a 1:1 mixture of demetalated material and a new product. Washing of the residue with petroleum ether left the pure aryllead compound **4.12**. It was subsequently found that the optimal conditions for formation of the aryllead were conducting the reaction at r.t. in freshly distilled dichloromethane in the presence of freshly dried lead tetraacetate and in the absence of light. Under these conditions aryllead **4.12** was isolated in 93 % yield (Figure 4.26).



Reagents and yield: (a) $\text{Pb}(\text{OAc})_4$, cat $\text{Hg}(\text{OAc})_2$, CH_2Cl_2 , r.t., 93 %.

Figure 4.26 Preparation of aryllead tricarboxylate **4.12**.

Although full spectroscopic data could not be obtained for this compound as a result of decomposition under mass spectroscopic analysis and limited solubility in suitable NMR

solvents, the ^1H NMR spectrum is quite diagnostic (Figure 4.27). In particular, the aromatic signal at δ 6.8 ppm has characteristic ^{207}Pb -satellites at 93 Hz either side of the parent peak.¹¹⁰

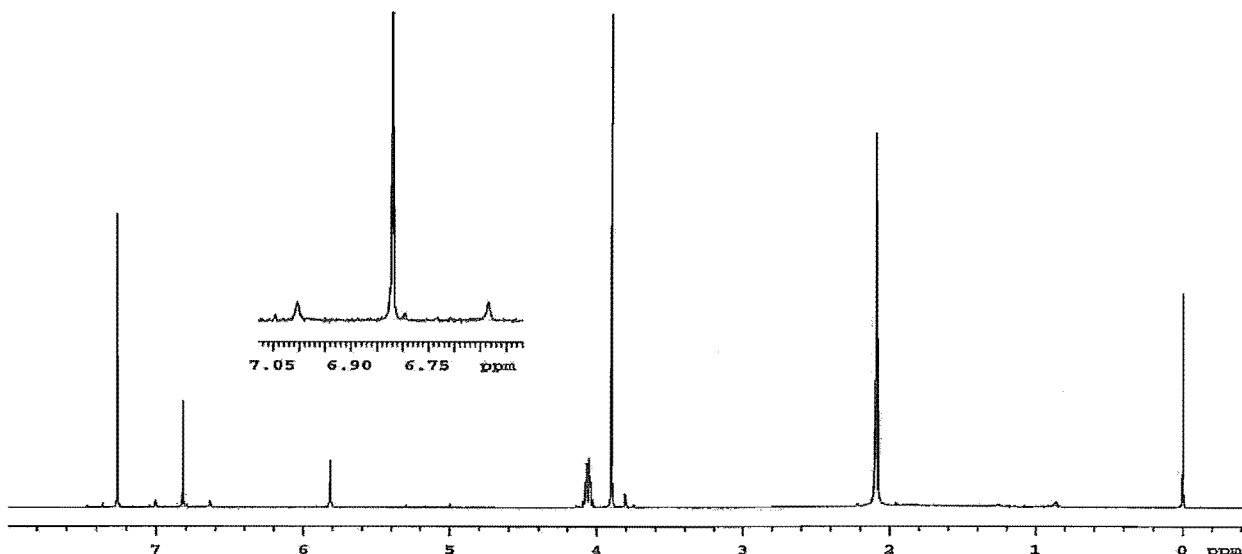
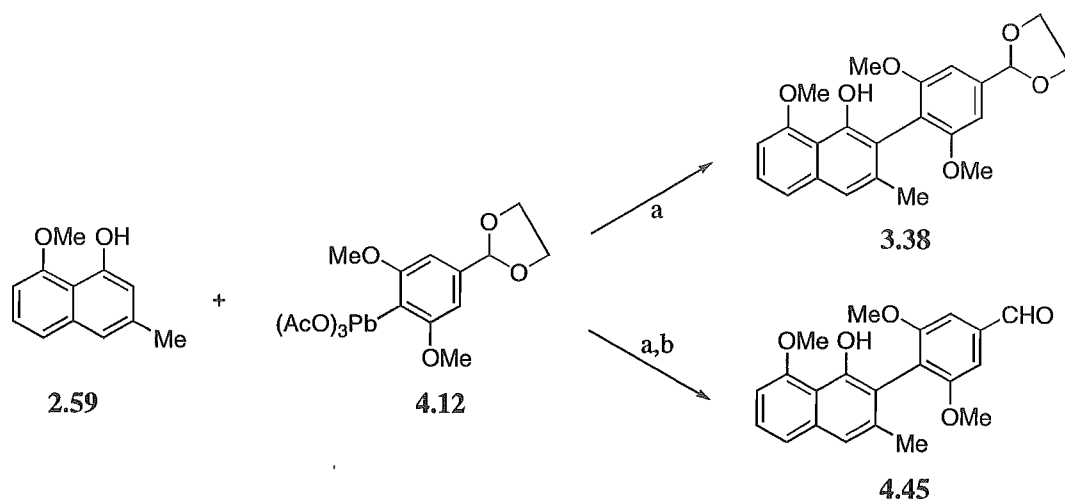


Figure 4.27 500 MHz ^1H NMR spectrum of aryllead tricarboxylate 4.41.

4.3.3 Formation of a 7-3'-Biaryl bond

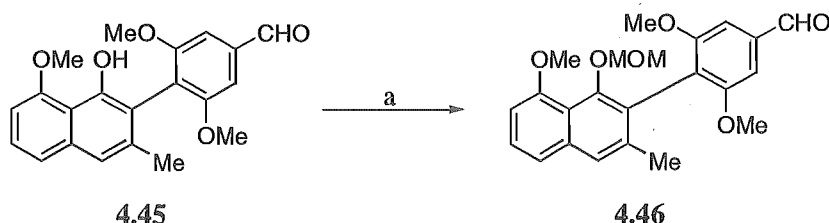
With sufficient quantities of an aryllead triacetate available, studies on the coupling of this compound with naphthol **2.59** were investigated. Stirring a solution of aryllead triacetate **4.12** with naphthol **2.59** and pyridine in dichloromethane resulted in the formation of a new product almost immediately, as detected by TLC analysis. Purification by column chromatography gave the *ortho*-arylated naphthol **3.38** in 64 % yield (Scheme 4.13). This was a very pleasing result given the problems encountered with previous attempts at formation of this key bond, along with the mild conditions, which gave rise to this extremely sterically demanding coupling. Following this, acetal **3.38** was readily deprotected by stirring in THF/aqueous sulfuric acid. This could also be achieved without purification of the intermediate acetal and resulted in formation of aldehyde **4.45** in 67 % yield over 2 steps.



Scheme 4.13 Reagents and yields: (a) pyridine, CH_2Cl_2 , r.t., 64 %; (b) aq $\text{H}_2\text{SO}_4/\text{THF}$, r.t., 67 % for 2 steps.

4.3.4 Non-stereoselective Synthesis of Ancistrocladidine

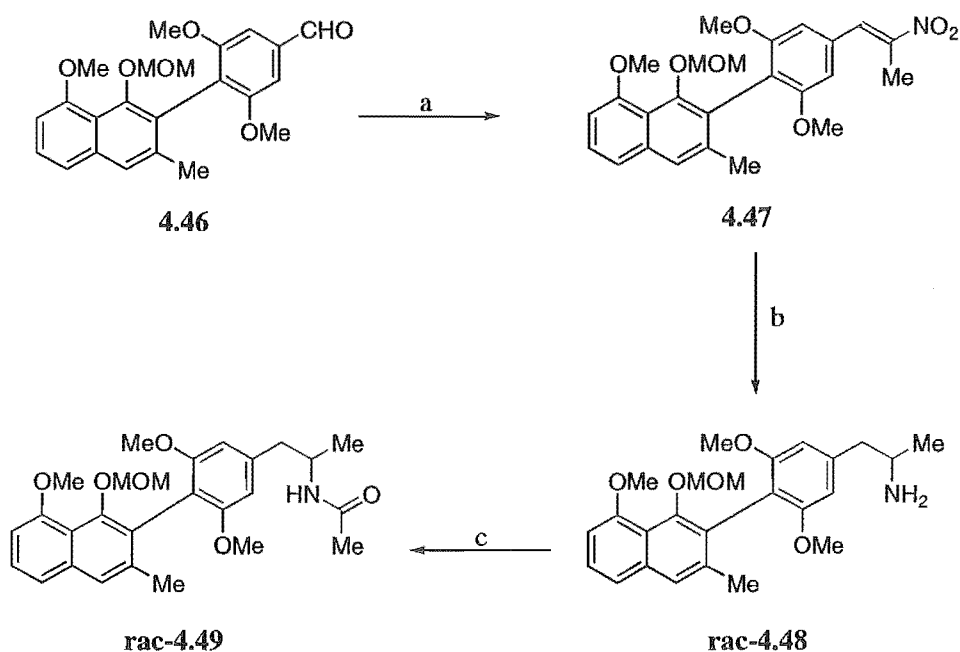
It was deemed appropriate to investigate a short non-stereoselective route to the natural product in order to assess the effects of the rather harsh conditions of a Bischler-Napieralski cyclisation on the rest of the molecule. In order to circumvent any problems associated with the presence of a free naphthol, it was protected as its methoxymethyl ether. As a result of the hindered nature of the naphthol, protection could not be achieved using either triethylamine or Hünig's base and methoxymethyl chloride. However, the protection proceeded smoothly by deprotonation of naphthol 4.45 using sodium hydride in THF, followed by addition of methoxymethyl chloride, which gave biaryl aldehyde 4.46 in 81 % yield (Figure 4.28).



Reagents and yield: (a) NaH , THF, MOM-Cl, r.t., 81 %.

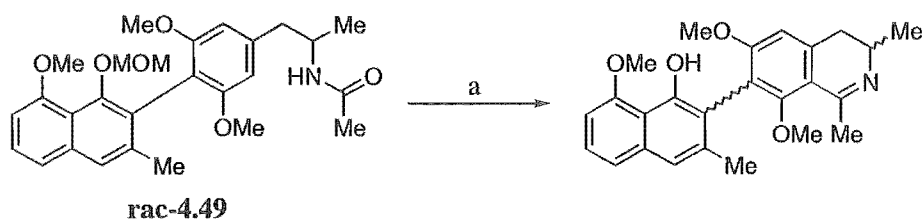
Figure 4.28 Protection of naphthol 4.45.

A Henry reaction on aldehyde **4.46** provided nitrostyrene **4.47** in 92 % yield. Subsequent reduction of the nitrostyrene **4.47** with lithium aluminium hydride in THF at reflux gave amine **rac-4.48** in 96 % yield, which upon treatment with acetyl chloride and triethylamine in dichloromethane gave acetamide **rac-4.49** in 97 % yield (Scheme 4.14).



Scheme 4.14 Reagents and yields: (a) EtNO_2 , NH_4OAc , HOAc , reflux, 92 %; (b) LiAlH_4 , THF, reflux, 96 %; (c) CH_3COCl , NEt_3 , CH_2Cl_2 , 0 °C to r.t., 97 %.

Attempted Bischler-Napieralski cyclisation of the acetamide, by treatment with POCl_3 in acetonitrile, resulted in a complex mixture of products, as well as production of large amounts of insoluble material. Repeating the cyclisation procedure in the presence of the acid scavenger 2,4,6-collidine, resulted in a much cleaner reaction. Interestingly, in the ^1H NMR spectrum of the crude reaction workup showed two peaks at δ 9.59 and 9.61 ppm. These were indicative of hydrogen bound naphthol protons, and indeed purification of the resulting products revealed that cleavage of the methoxymethyl protecting group had occurred, giving the natural product, albeit as a racemic mixture of diastereoisomers (Figure 4.29).



Reagents and yield: (a) POCl_3 , 2,4,6-collidine, CH_3CN , reflux, 74 %.

Figure 4.29 Cyclisation/deprotection to give the natural product.

Atropisomers are produced in the above reaction as a consequence of the loss of symmetry upon cyclisation as depicted earlier in **Figure 4.24**. As the stereochemistry of the C3 methyl group wasn't set, each of the aforementioned atropisomers will also be accompanied by their respective enantiomers as shown in **Figure 4.30**.

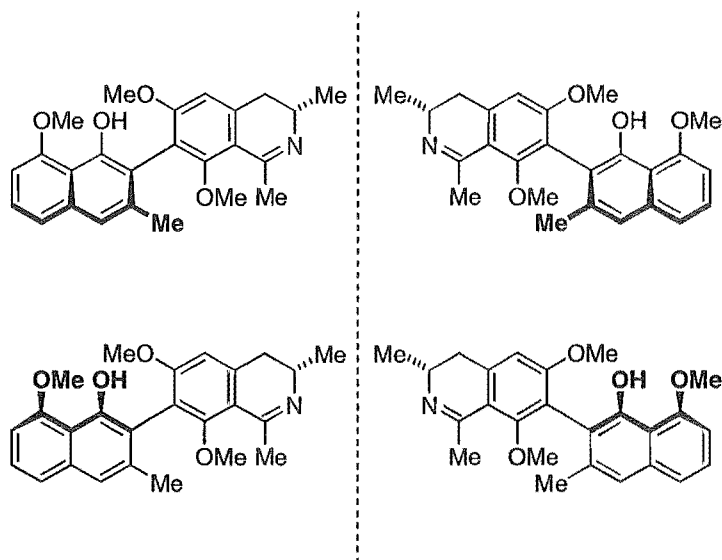
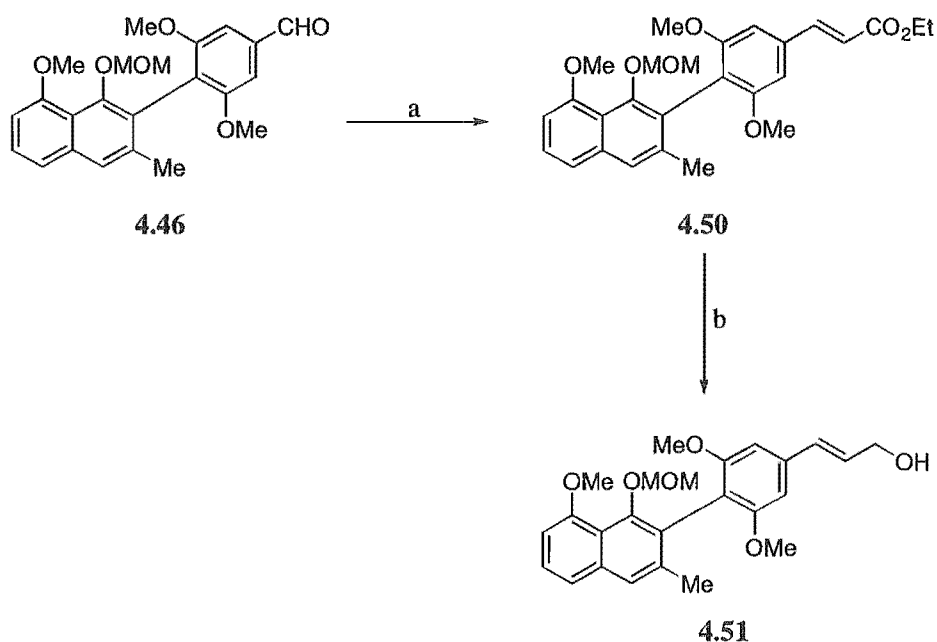


Figure 4.30 Stereoisomers of Ancistrocladidine.

4.3.5 Enantioselective Synthesis of Ancistrocladidine

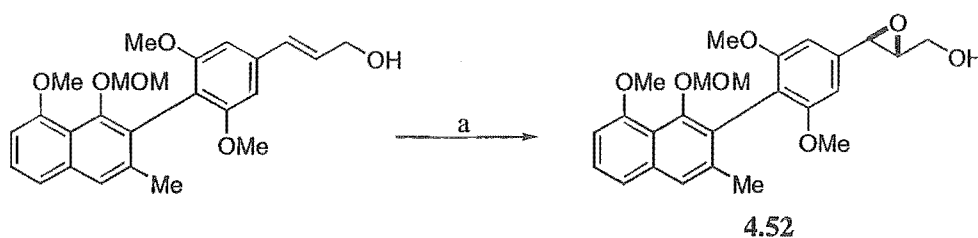
Accordingly, the next avenue of investigation was an enantioselective synthesis of ancistrocladidine **1.99**. The stereochemistry of the C3 methyl group would be set using the previously explored epoxidation methodology. A Horner-Wadsworth-Emmons reaction on

aldehyde **4.46** gave ester **4.50** in quantitative yield. Subsequent reduction of ester with DIBAL in dichloromethane proved problematic, with significant deprotection of the methoxymethyl ether accompanying the desired reduction. Even at $-78\text{ }^{\circ}\text{C}$ a significant amount of deprotected material was produced. However, it was found that conducting the reduction in toluene gave a much cleaner reaction, resulting in isolation of allylic alcohol **4.51** in 89 % yield (Scheme 4.15).



Scheme 4.15 Reagents and yields: (a) $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, NaH, benzene, $0\text{ }^{\circ}\text{C}$ to r.t., 100 %; (b) DIBAL, toluene, $-78\text{ }^{\circ}\text{C}$, 89 %.

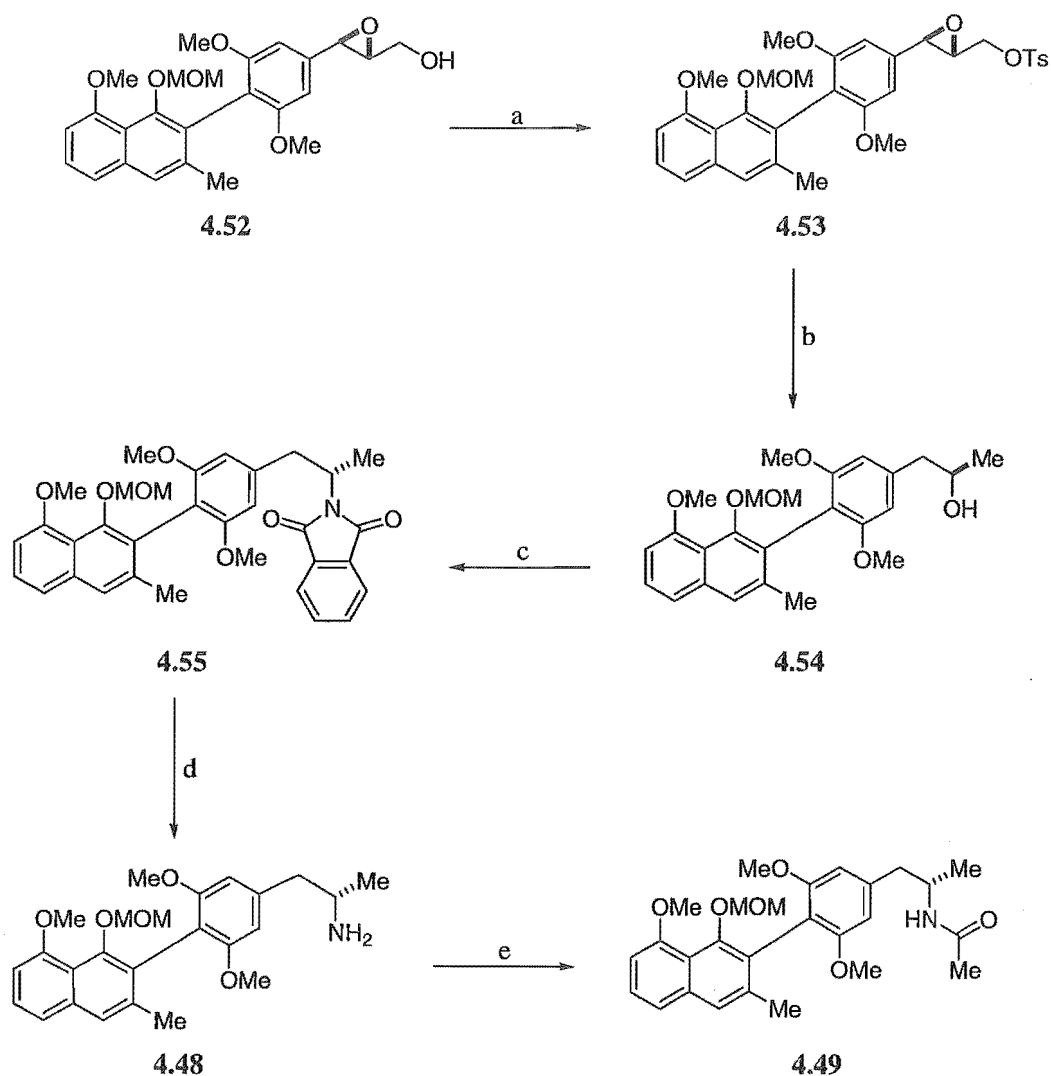
Asymmetric epoxidation of the allylic alcohol proceeded smoothly to give epoxide **4.52** in 80 % yield and 90 % ee (Figure 4.31). Recrystallisation from toluene/petroleum ether gave the epoxide in 63 % yield and $>95\text{ }^{\circ}\text{ee}$. The molecule contains two elements of stereochemistry - the biaryl axis and the epoxide stereochemistry - only that of the epoxide is set so the possibility of a complicated NMR spectrum exists as a result of diastereoisomers. Interestingly, only the aromatic CH's on the epoxide half of the molecule showed any splitting (0.005 ppm) in the ^1H NMR spectrum of epoxide **4.52**.



Reagents and yield: (a) $\text{Ti}(\text{O}i\text{-Pr})_4$, $t\text{-BuOOH}$, (*D*)-(-)-diisopropyltartrate, 4Å sieves, CH_2Cl_2 , -20°C , 80 %, 90 % ee.

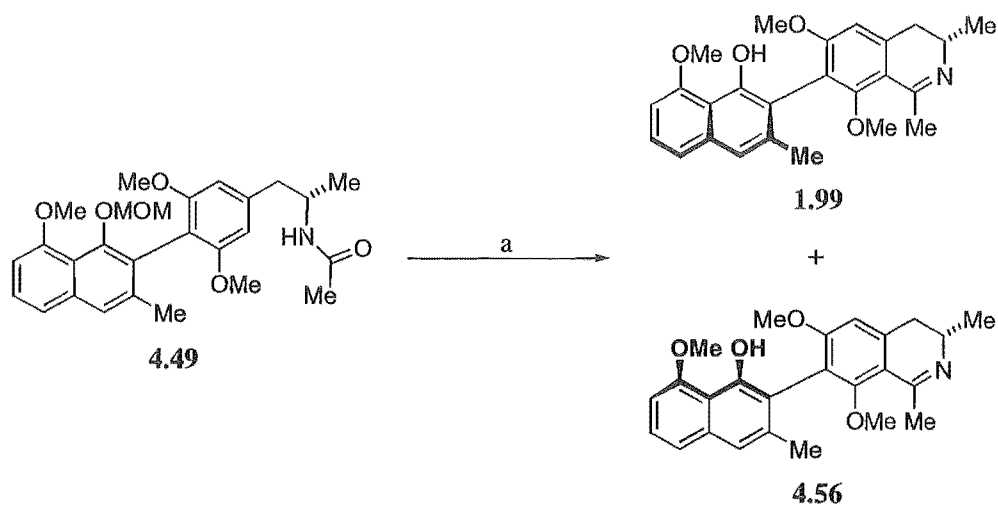
Figure 4.31 Sharpless asymmetric epoxidation of the allylic alcohol.

With the stereochemistry now set the required nitrogen functionality could be introduced. Tosylate **4.53** was prepared in 83 % yield by reaction of alcohol **4.52** with *p*-toluenesulfonyl chloride, triethylamine, and DMAP in dichloromethane. It was observed earlier that the methoxymethyl protecting group was cleaved on exposure to DIBAL in dichloromethane, so alternative conditions were explored for the reductive ring opening of the epoxide. It has been shown that reduction with lithium aluminium hydride in ether also gives good regioselectivity in the ring opening of such epoxides.¹²⁰ Accordingly, reduction of tosylate **4.53** with this combination of reagents gave alcohol **4.54** in 94 % yield. Following this, Mitsunobu inversion with phthalimide in the presence of PPh_3 and DEAD gave imide **4.55**. However, there were difficulties encountered in the purification of this compound. 1,2-Dicarbethoxyhydrazine ($\text{EtO}_2\text{CNHNHCO}_2\text{Et}$), a by-product from the Mitsunobu reaction, co-eluted with the imide on silica gel. Fortunately, this impurity could be readily removed by running the compounds through a short alumina column, prior to purification on silica gel. Purification by this protocol afforded the imide in 82 % yield. Imide **4.55** was readily deprotected by refluxing in an aqueous ethanolic solution of methylamine to give amine **4.48** in quantitative yield. The acetylation was carried out as described for the racemate and gave amide **4.49** in almost quantitative yield (Scheme 4.16).



Scheme 4.16 Reagents and yields: (a) TsCl, NEt₃, DMAP, CH₂Cl₂, 0 °C, 83 %; (b) LiAlH₄, Et₂O, 0 °C to r.t., 94 %; (c) Phthalimide, PPh₃, DEAD, THF, 0 °C to r.t., 82 %; (d) MeNH₂, H₂O/EtOH, reflux; 100 %; (e) CH₃COCl, NEt₃, CH₂Cl₂, 0 °C to r.t., 97 %.

All that remained was the cyclisation/deprotection step to give the natural product **1.99**, along with its diastereomeric atropisomer **4.56**. Indeed, reaction with POCl₃/2,4,6-collidine gave a 1:1 mixture of the diastereoisomers (as determined by ¹H NMR spectroscopy) in 74 % yield (Figure 4.32).



Reagents and yield: (a) POCl_3 , 2,4,6-collidine, CH_3CN , reflux, 74 %.

Figure 4.32 Cyclisation to give the natural product and its diastereoisomer.

As expected the above compounds exhibit very similar spectroscopic properties as is exemplified below by the ^1H NMR spectrum of the mixture of diastereoisomers (**Figure 4.33**).

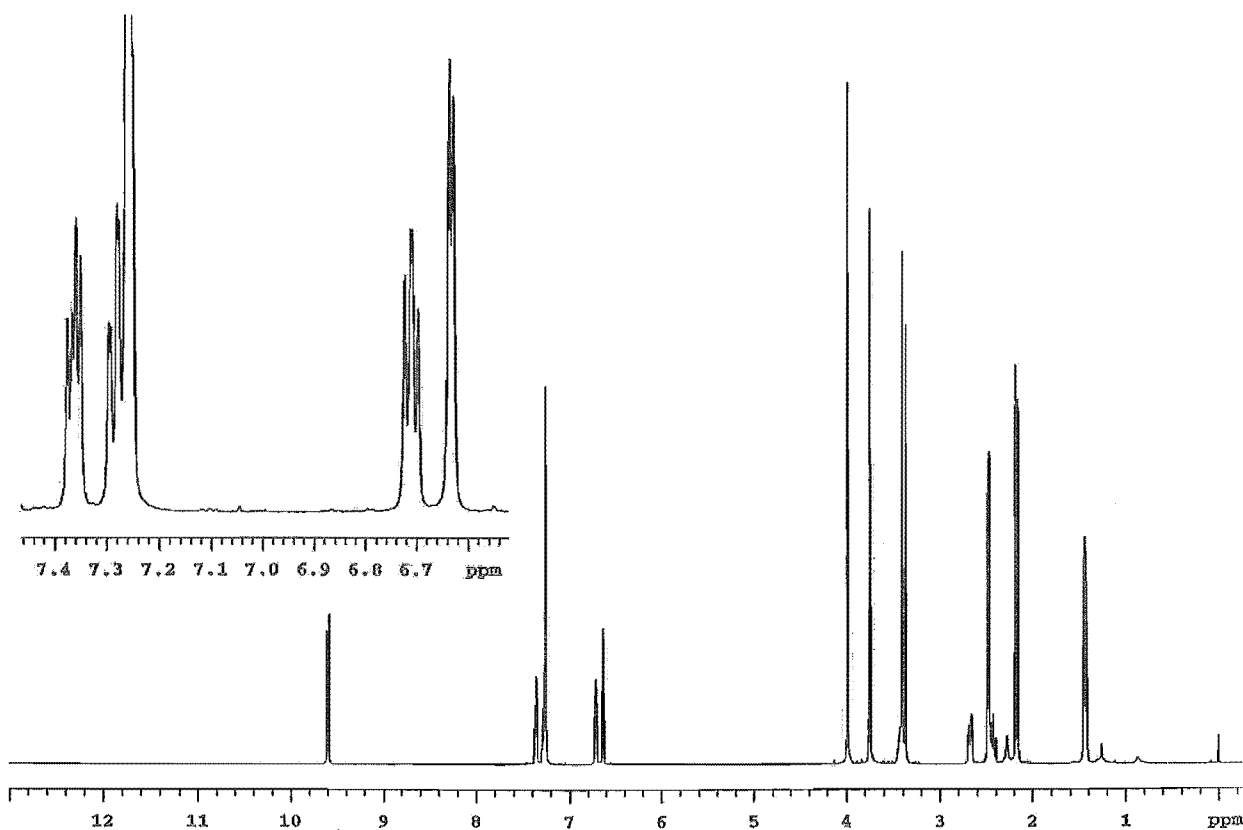


Figure 4.33 500 MHz ^1H NMR spectrum of a mixture of atropisomers **1.99** and **4.56**.

In order to provide the necessary proof that the natural product had indeed been synthesised it was necessary to separate the above compounds. Surprisingly, chromatography using alumina provided fractions that revealed significant diastereomeric enrichment as detected by ^1H NMR spectroscopy. Pleasingly, crystallisation of a fraction enriched with the natural isomer gave a pure sample of the natural product (**Figure 4.34**).

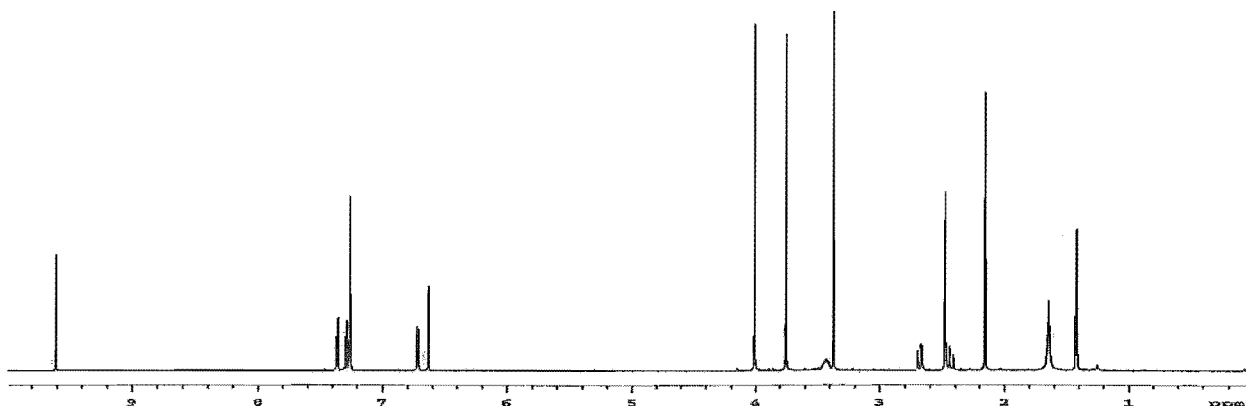


Figure 4.34 500 MHz ^1H NMR spectrum of synthetic ancistrocladidine **1.99**.

Surprisingly, attempted crystallisation of a fraction enriched in the non-natural isomer also gave crystals of the natural product. It was subsequently found that pure natural product could be obtained by directly crystallising the 1:1 mixture of diastereoisomers obtained from the reaction. This left the mother liquor enriched in the non-natural isomer, which after repeated crystallisations afforded the unnatural isomer **4.56** with 90 % diastereomeric purity (**Figure 4.35**).

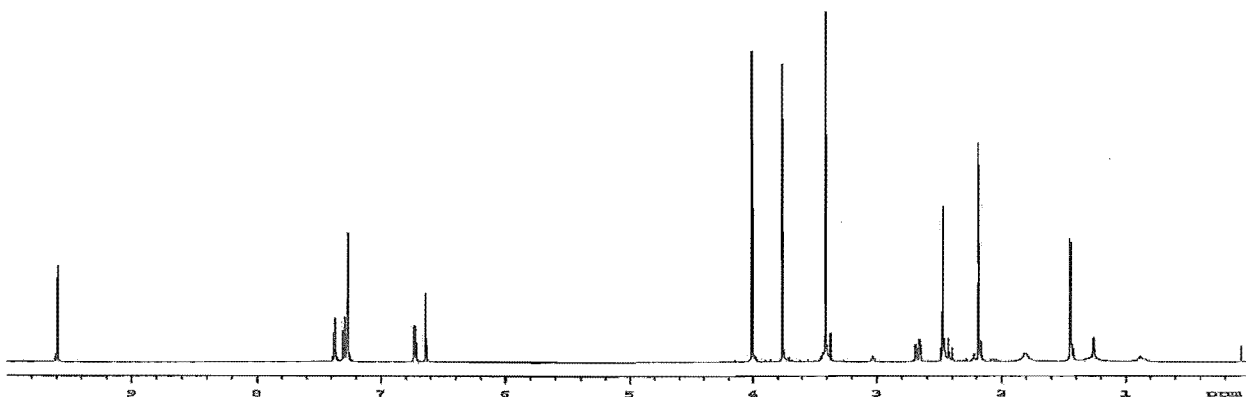
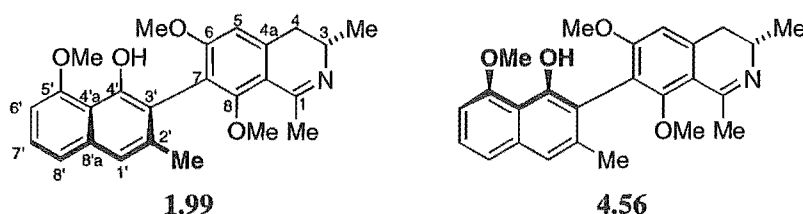


Figure 4.35 500 MHz ^1H NMR spectrum of atropisomer **4.56** of 90 % diastereomeric purity.

4.3.6 Properties of Ancistrocladidine

Unfortunately, an authentic sample of the natural product for comparative purposes was not available.¹³¹ However, a paper reporting the unambiguous assignment of the ^1H and ^{13}C NMR spectra, along with other relevant data had been published. Synthetic ancistrocladidine gave good agreement for the mass spectroscopic, infrared, optical rotation, and melting point data reported for the natural material isolated by Cordell *et al.* (Figure 4.36).



	ANCISTROCLADIDINE		
	Natural	Synthetic (1.99)	Atropisomeric (4.56)
M⁺	405 (EI)	405.1940 (HRMS)	405.1940 (HRMS)
MP (°C)	255-258 °C DEC ⁴³ 245-247 °C DEC ⁴⁰	253-254 °C DEC	viscous oil
[α]_D²⁰	- 129.7 (c 0.064, CHCl ₃) ⁴³ - 149.73 (c 1.13, CHCl ₃) ⁴⁰	-136 (c 1.84, CHCl ₃)	+ 40.4 (c 0.292, CHCl ₃)
Infrared (cm ⁻¹)	3367, 3013, 2934, 1609, 1090	3368, 3012, 2934, 1609, 1090	3381, 2934, 1593, 1090

Figure 4.36 Properties of ancistrocladidine and its atropisomer.

Examination of the ^1H NMR spectrum of synthetic ancistrocladidine revealed a minor discrepancy in the coupling constant quoted for H 4 β (Table 4.1). For the natural product the doublet of doublets at 2.42 ppm was reported to have coupling constants of 15.5 and 1.8 Hz, whereas for synthetic ancistrocladidine coupling constants of 15 and 13 Hz were observed. For related 3,4-dihydroisoquinolines it has been reported that coupling constants were typically 16 and 10 Hz.¹³² Also, it should be noted that the coupling constants for the iododihydroisoquinoline 4.14, prepared in this thesis, were 16 and 13 Hz for the H β signal. Personal communication with Professor Cordell revealed that the coupling constant quoted for the natural product was indeed a misprint.

	ANCISTROCLADIDINE		
	Natural	Synthetic (1.99)	Atropisomeric (4.56)
¹H NMR	δ (360 MHz, CDCl ₃) 9.63 (1H, s, OH) 7.36 (1H, d, J = 7.3 Hz, H-8') 7.28 (1H, t, J = 7.3 Hz, H-7') 7.25 (1H, s, H-1') 6.71 (1H, d, J = 7.3 Hz, H-6') 6.63 (1H, s, H-5) 3.99 (3H, s, 5'-OMe) 3.75 (3H, s, 6-OMe) 3.41 (1H, m, H-3) 3.37 (3H, s, 8-OMe) 2.69 (1H, dd, J = 15.5, 4.5 Hz, H-4 α) 2.49 (3H, d, J = 1.8 Hz, 1-Me) 2.42 (1H, dd, J = 15.5, 1.8 Hz, H-4 β) 2.16 (3H, s, 2'-Me) 1.43 (3H, d, J = 6.7 Hz, 3-Me)	δ (500 MHz, CDCl ₃) 9.61 (1H, s) 7.36 (1H, d, J = 8.3 Hz) 7.28 (1H, dd, J = 8.3, 7.3 Hz) 7.25 (1H, s) 6.72 (1H, d, J = 7.3 Hz) 6.63 (1H, s) 4.01 (3H, s) 3.75 (3H, s) 3.43 (1H, m) 3.37 (3H, s) 2.68 (1H, dd, J = 15, 4.4 Hz) 2.48 (3H, d, J = 2.0 Hz) 2.45 (1H, dd, J = 15, 13 Hz) 2.16 (3H, s) 1.42 (3H, d, J = 6.8 Hz)	δ (500 MHz, CDCl ₃) 9.59 (1H, s) 7.37 (1H, d, J = 8.3 Hz) 7.29 (1H, dd, J = 8.3, 7.3 Hz) 7.27 (1H, s) 6.73 (1H, d, J = 7.3 Hz) 6.64 (1H, s) 4.01 (3H, s) 3.76 (3H, s) 3.41 (1H, m) 3.41 (3H, s) 2.67 (1H, dd, J = 16, 4.4 Hz) 2.47 (3H, d, J = 2.0 Hz) 2.43 (1H, dd, J = 15, 14 Hz) 2.19 (3H, s) 1.44 (3H, d, J = 6.8 Hz)
¹³C NMR	δ (90.8 MHz, CDCl ₃) 163.26 (C-1) 159.28 (C-6) 157.75 (C-8) 156.01 (C-5') 151.26 (C-4') 141.25 (C-4a) 137.71 (C-2') 136.08 (C-8'a) 125.58 (C-7') 121.07 (C-8') 118.70 (C-1') 118.63 (C-7) 116.93 (C-8a) 116.79 (C-3') 113.25 (C-4'a) 105.87 (C-5) 103.01 (C-6') 60.82 (8-OMe) 55.93 (6-OMe) 55.80 (5'-OMe) 51.40 (C-3) 35.20 (C-4) 26.85 (1-Me) 21.93 (3-Me) 20.46 (2'-Me)	δ (126 MHz, CDCl ₃) 163.1 159.2 157.7 156.1 151.3 141.3 137.8 136.2 125.6 121.1 118.8 118.7 117.1 116.9 113.3 105.9 103.1 60.9 56.0 55.8 51.5 35.2 26.9 22.0 20.5	δ (126 MHz, CDCl ₃) 163.2 159.3 157.7 156.1 151.1 141.5 138.0 136.2 125.6 121.3 118.9 118.8 117.3 117.0 113.3 105.9 103.1 61.2 56.0 55.9 51.5 35.3 26.6 22.4 20.6

Table 4.1 ¹H and ¹³C NMR properties of ancistrocladidine and its atropisomer.

4.3.7 Summary

The highly hindered 7-3' biaryl bond, found in the naphthylisoquinoline alkaloid ancistrocladidine, has been formed by direct coupling of an aryllead triacetate with 8-methoxy-3-methyl-1-naphthol. An enantioselective synthesis of the natural product was then achieved, using a Sharpless asymmetric epoxidation to set the desired stereochemistry. Aside from a minor discrepancy for a coupling constant, which was later found to be a misprint, the data for the natural material is in good agreement with that for synthetic ancistrocladidine. To the best of the authors' knowledge this represents the first total synthesis of a 7-3'-linked naphthylisoquinoline alkaloid.

Chapter Five

Summary and Future Studies

5.1 Summary

In a study that has resulted in an enantioselective total synthesis of ancistrocladidine **1.99**, a 7-3'-linked naphthylisoquinoline alkaloid, several key issues were addressed. As a result of previous synthetic work carried out in the area of naphthylisoquinoline alkaloid total synthesis, a number of useful methods had emerged for synthesis of the naphthalene portion, as discussed in Chapter 1. However, it was noted that few of the methods proved widely applicable and accordingly Chapter 2 details the development of a new naphthalene synthesis. It was stated that in order for it to be useful it should proceed *via* intermediates, which would allow flexibility in the introduction of functionality, in particular at positions that are substituted with respect to the naphthylisoquinoline alkaloids. The initial synthetic strategy was based on the work of Wallace *et al* who had shown that benzocyclobutenones are versatile precursors to substituted tetralones and naphthalenes. It was envisaged that this strategy could be adapted to allow for the development of a synthesis of 1,8-dioxygenated naphthalenes. This synthetic approach required access to 6-alkoxybenzocyclobutenones. Based on the well documented $[2\pi + 2\pi]$ cycloaddition reaction an efficient large-scale synthesis of 6-alkoxybenzocyclobutenones was developed proceeding in 3 steps from readily available compounds (**Figure 5.1**).⁷⁷

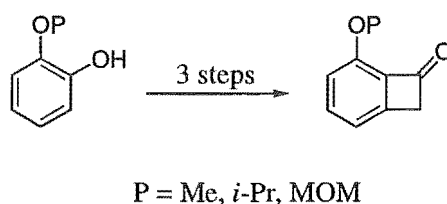


Figure 5.1 Preparation of 6-alkoxybenzocyclobutenones.

Following this, functionalisation of these intermediates to provide useful naphthalene building blocks was pursued. Selective bromination of benzocyclobutenones **2.12** and **2.29** was readily achieved and accordingly elaboration of the rest of the naphthalene moiety was examined. 1,8-Dihydroxynaphthalene **2.44**, a key intermediate for the synthesis of the natural product palmarumycin CP1, was readily prepared by cyclisation of the appropriate ethynylbenzocyclobutenol **2.45**. However, extension of this methodology to enable a synthesis of 3-methylsubstituted naphthalenes, *via* the cyclisation of propynylbenzocyclobutenols, gave a mixture of products. Upon consideration of possible mechanisms to account for the production

of an indanone by-product **2.48**, an alternative cyclisation protocol was designed. The desired allenic precursors were prepared by a two-step procedure involving hydroxyl-directed reduction of the propargyl chlorides. Pleasingly, thermolysis of the allenic alcohols gave the desired naphthalenes in good yields. A range of useful naphthalene building blocks were then prepared as summarised below (**Figure 5.2**).⁷⁸

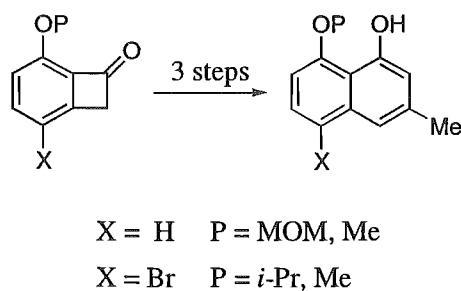


Figure 5.2 Preparation of some functionalised naphthalenes.

In Chapter 3 investigations were carried out regarding the use of benzocyclobutenones as key intermediates for the formation of the biaryl bond present in ancistrocladidine. The initial approach was based upon synthesis and cyclisation of a 1,1-disubstituted allene. Two strategies were investigated for synthesis of this allene, firstly a palladium-catalysed approach and secondly, an approach based on addition of an allenyllithium species to benzocyclobutenone **2.12**. Within these two strategies either the entire dihydroisoquinoline portion could be carried through the sequence, or a suitable precursor could be used. However, attempted functionalisation of the entire heterocyclic moieties **rac-1.5** or **rac-3.8** by directed *ortho*-metalation failed (**Figure 5.3**).

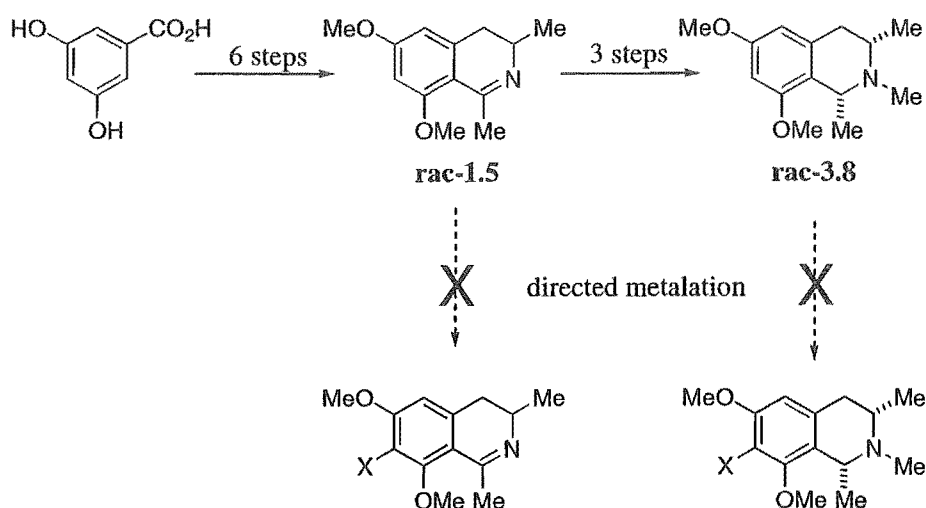


Figure 5.3 Attempted functionalisation of the dihydro- and tetrahydroisoquinolines.

As a result of this a suitably functionalised precursor **3.6** was synthesised according to literature procedures and subsequent studies were performed using derivatives of this compound (**Figure 5.4**).

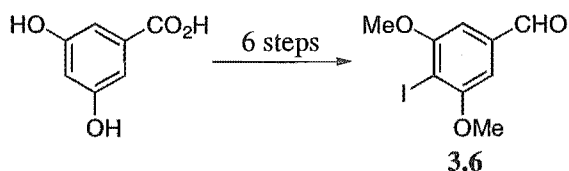


Figure 5.4 Literature preparation of functionalised intermediate **3.6**.

Investigation of the palladium-based approach did give a small amount of the desired allene **3.22** but not surprisingly, the major product from this reaction was acetylene **3.21** resulting from reductive elimination of a less hindered propargyl species. It was suggested that perturbation of this equilibrium, in order to favour reductive elimination of an allenic product, was not likely based on steric grounds. Following this, studies toward synthesis of an appropriate allenyllithium precursor were undertaken. Acetylenic functionality was introduced using the Sonogashira reaction, however an attempted S_N2' reduction to produce allenes was unsuccessful as a result of the ensuing sterically favoured S_N2 reduction, which resulted in acetylene formation (**Figure 5.5**).

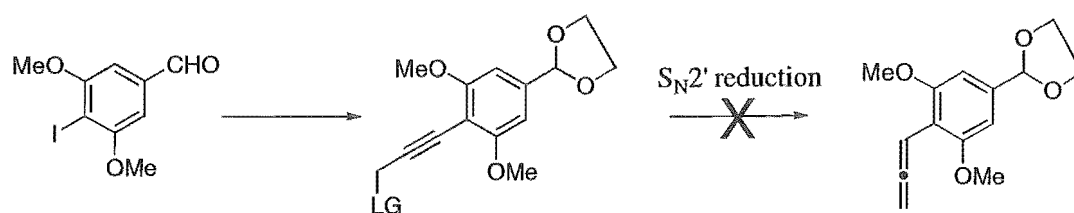


Figure 5.5 Attempted synthesis of an allenyllithium precursor.

There was evidence to suggest that isomerisation of a propargyl stannane under palladium catalysis may lead to formation of an allenyl stannane. However the resulting palladium-catalysed stannylation resulted only in the formation of a propargylacetylene (**Figure 5.6**).

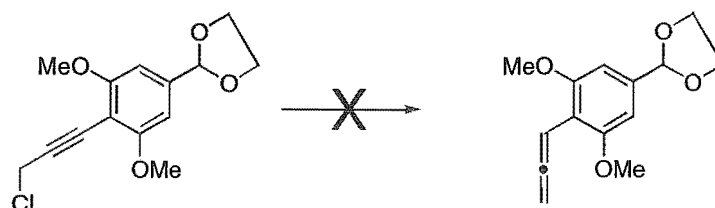


Figure 5.6 Attempted synthesis of an allenyl stannane.

At this point the strategy was re-evaluated in order to incorporate a palladium-catalysed hydrostannylation, which had been shown to favour formation of sterically demanding products. It was believed that the lithiospecies derived from this stannane could be added to benzocyclobutenone **2.12**, following which thermolysis of the resulting benzocyclobutenol would yield a tetralone, which could be converted into a naphthol. The hydrostannylation was successful giving the desired organometallic, which following protection, underwent transmetalation to an organolithium species. Unfortunately, no reaction could be induced between the so derived lithiospecies and the benzocyclobutenone. It was thought that the methoxymethyl protecting group may be contributing to the formation of a very hindered nucleophile. Accordingly, an alternative stannane was synthesised which contained a methyl group at the position formally occupied by the protecting group. However, the lithiospecies derived from this stannane failed to react with the benzocyclobutenone. A chromium complex **3.51** of benzocyclobutenone **2.12** was prepared, as previous work had shown that such complexes exhibited a greater affinity for reactions with nucleophiles when compared to the uncomplexed species. No reaction resulted between complex **3.51** and either lithiospecies. It

was concluded that the combination of a hindered lithiospecies with a benzocyclobutenone was not compatible for the synthesis of such a highly hindered bond (Figure 5.7).

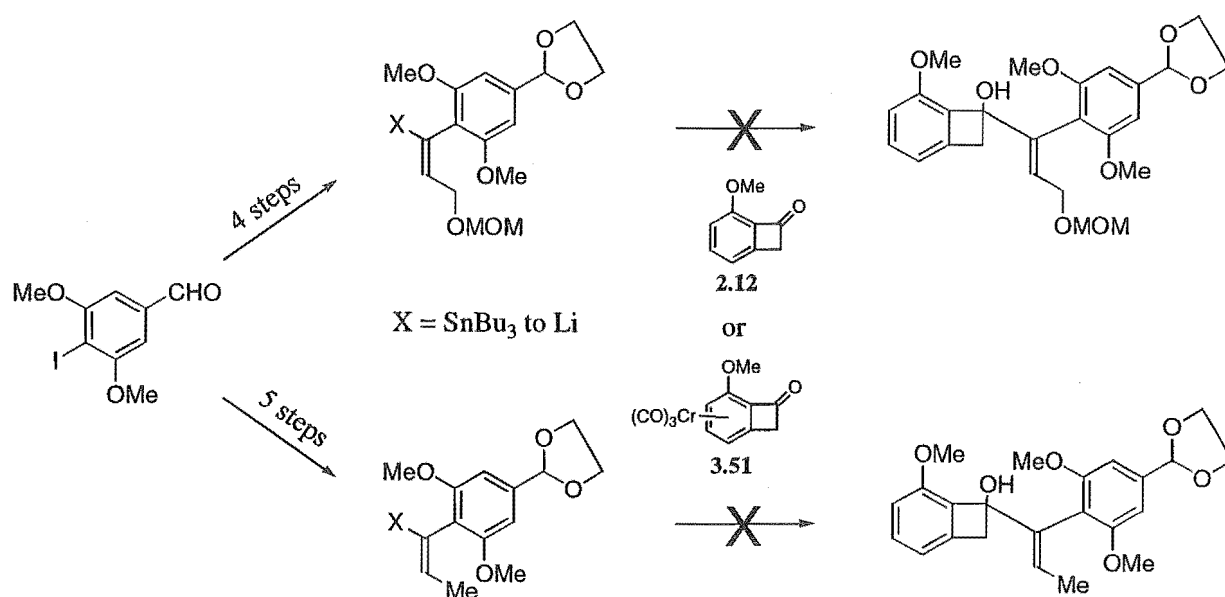


Figure 5.7 Attempted formation of the 7-3' biaryl bond.

In Chapter 4 an alternative strategy was discussed involving assembly of the naphthalene moiety prior to biaryl bond formation. It was suggested that a lead-mediated *ortho*-arylation approach had merit. In particular, the direct coupling of naphthol **2.59** and the 3,4-dihydroisoquinoline had the potential to be adapted to allow stereocontrol in the formation of the biaryl bond. A short non-stereoselective synthesis of functionalised 3,4-dihydroisoquinoline *rac*-**4.14** was carried out, which allowed the iodide moiety to be successfully carried through the synthesis. This strategy was adapted to allow an asymmetric synthesis of both 3,4-dihydro- and tetrahydroisoquinoline building blocks **4.13** and **4.14** (Figure 5.8).

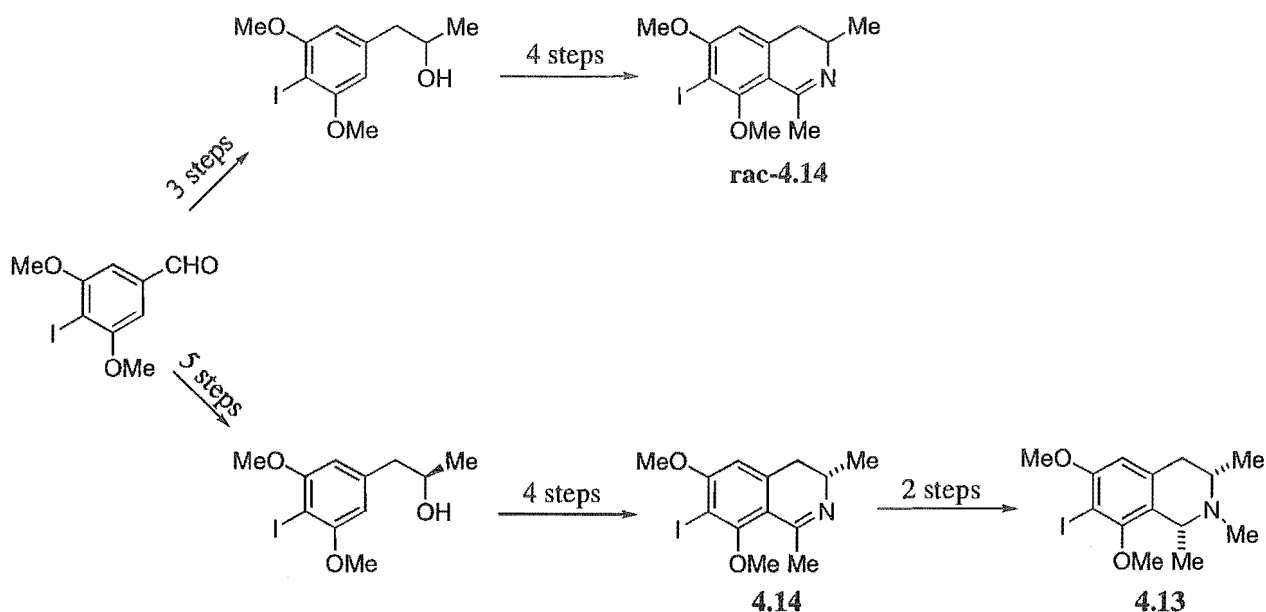


Figure 5.8 Preparation of functionalised heterocyclic building blocks.

The respective stannanes were prepared but unfortunately, the lead compounds of either species could not be synthesised. Relatively few aryllead compounds containing nitrogen are known, assumedly as a result of the reactivity of this atom towards lead containing species. A less convergent synthetic approach was adopted at this point involving assembly of the dihydroisoquinoline moiety after biaryl bond formation. This did not allow any stereocontrol in formation of the biaryl bond, but allowed formation of an aryllead species in the absence of nitrogen functionality. The desired aryllead tricarboxylate **4.12** was readily prepared in excellent yield from the iodide **3.6** prepared in Chapter 3. As a synthesis of the naphthol coupling partner had been developed in Chapter 2, the crucial biaryl-coupling could be investigated (Figure 5.9).

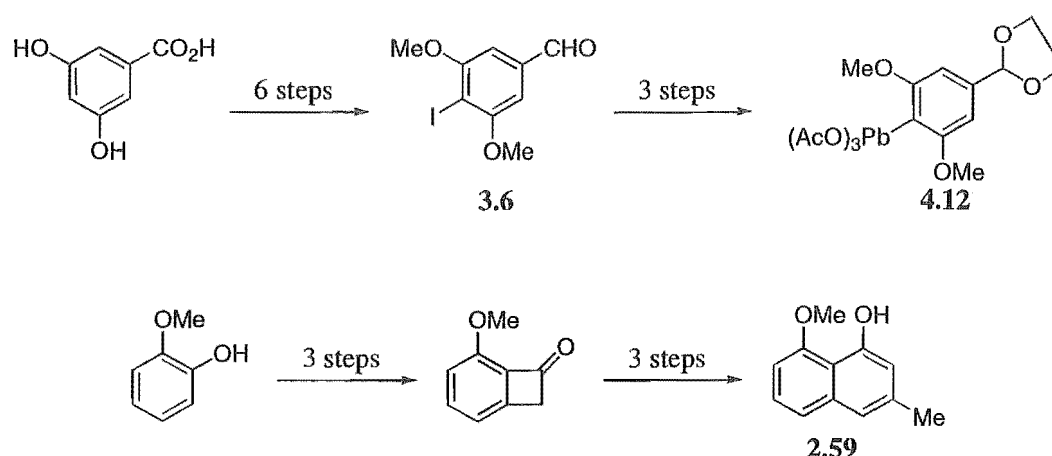


Figure 5.9 Synthesis of the biaryl-coupling precursors **2.59** and **4.12**.

Pleasingly, the ensuing *ortho*-arylation reaction of 8-methoxy-3-methyl-1-naphthol (**2.59**) by aryllead tricarboxylate **4.12** proceeded under extremely mild conditions. Following this a short non-stereoselective synthesis of the natural product was carried out, including a fortuitous deprotection under Bischler-Napieralski cyclisation conditions, which gave the natural product as a mixture of four isomers. An enantioselective synthesis was carried out utilising a Sharpless asymmetric epoxidation to set the desired stereochemistry. Overall, ancistrocladidine was prepared as a separable mixture of atropisomeric diastereoisomers *via* a synthesis that had a longest linear sequence of 21 steps from 3,5-dihydroxybenzoic acid. To the best of the authors knowledge this represents the first total synthesis of a naphthylisoquinoline alkaloid containing the rare, highly hindered 7-3' biaryl bond (**Figure 5.10**).

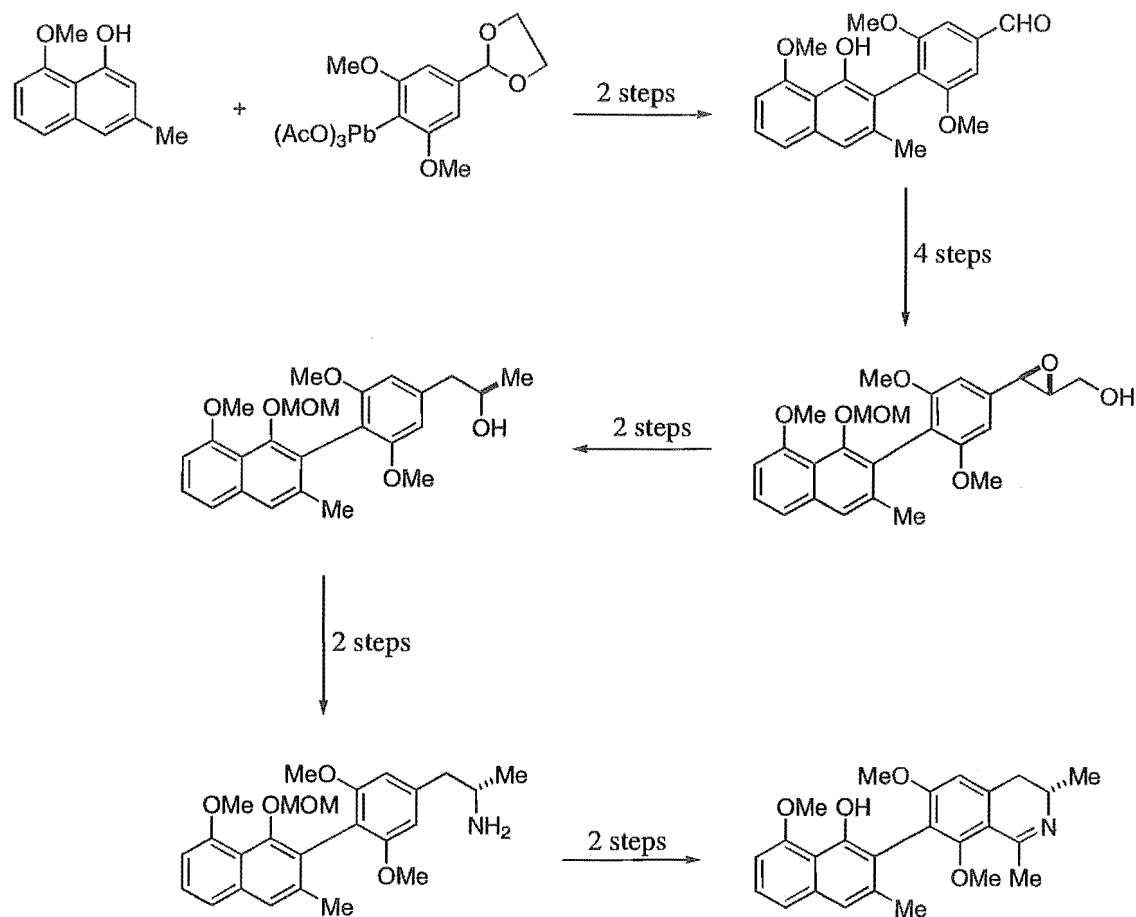


Figure 5.10 Enantioselective total synthesis of ancistrocladidine.

5.2 Future Studies

By embarking on studies culminating in a total synthesis of ancistrocladidine several useful results have emerged. These include development of efficient syntheses of 6-alkoxybenzocyclobutenones, which could be utilised in the synthesis of useful naphthalene building blocks. Following this, studies towards formation of the challenging 7-3' biaryl bond of ancistrocladidine **1.99** resulted in the emergence of *ortho*-arylation as suitable methodology. Many of the initial strategies required modification in order to achieve the desired results. However, this serves to reinforce the value of natural product synthesis as a tool for testing established synthetic methodology to its limit, as well as providing insights into how this methodology can be improved.

To this end a future prospect of this research is an investigation into the synthesis of other naphthylisoquinoline alkaloids utilising lead-mediated *ortho*-arylation. For example, dioncophylline B¹³³, a naphthylisoquinoline alkaloid that doesn't exhibit atropisomerism, could be generated from either A and B or C and D (Figure 5.11).

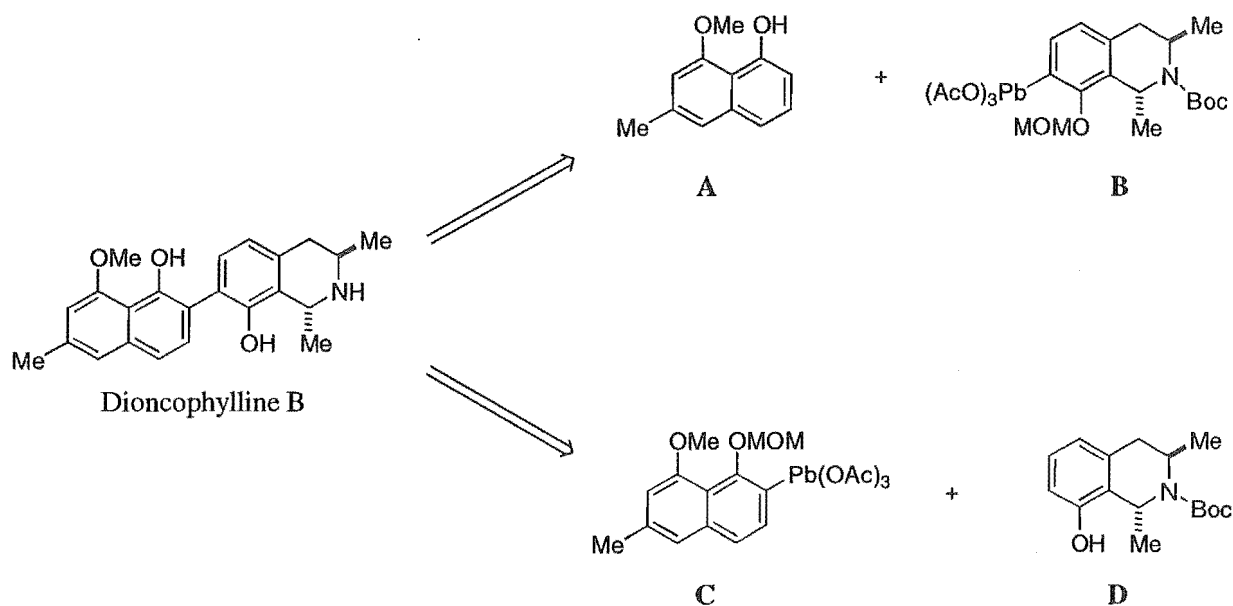


Figure 5.11 Retrosynthesis of dioncophylline B.

If this strategy proves to be successful, efforts could be turned to the synthesis of a naphthylisoquinoline alkaloid possessing axial chirality, such as dioncophylline A.¹³⁴ This would allow the asymmetric version of the reaction to be examined, which could lead to a diastereoselective synthesis (Figure 5.12).¹¹³

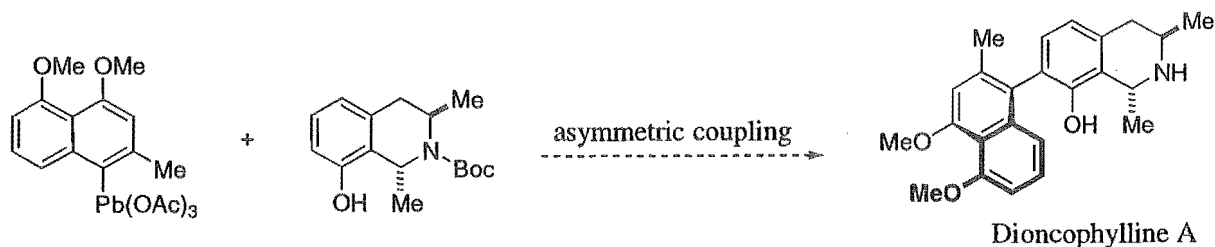


Figure 5.12 A possible asymmetric coupling.

Also a convergent diastereoselective total synthesis of both 7-3' naphthylisoquinoline alkaloids, ancistrocladidine **1.99** and ancistrotectorine **1.100** could be investigated (Figure 5.13). This was the aim of the initial work in Chapter 4, and accordingly, appropriately functionalised chiral dihydro- and tetrahydroisoquinoline building blocks were prepared. However, it was found that the requisite aryllead precursors could not be prepared.

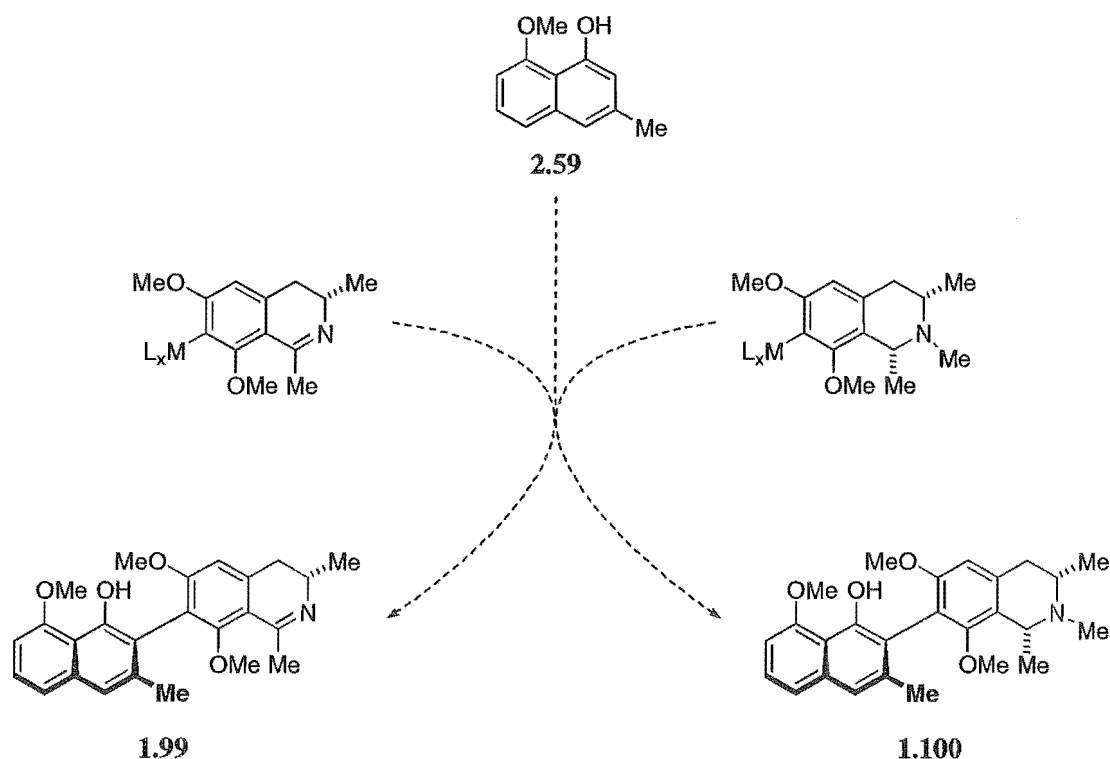


Figure 5.13 Convergent approach to ancistrocladidine and ancistrotectorine.

Other metals, for example titanium, have been used for reactions whose mechanism has been paralleled with that of *ortho*-arylation by lead compounds.¹³⁵ Accordingly a study that establishes the compatibility of other metals with the nitrogen functionality present in the dihydro- and tetrahydroisoquinoline moieties could lead to the ultimate prize in naphthylisoquinoline alkaloid synthesis, a convergent stereoselective total synthesis.

Chapter Six

Experimental

6.1 General Experimental

Unless otherwise stated all reactions were performed in dry glassware under an atmosphere of oxygen free nitrogen. All organic extracts were washed with brine and dried over anhydrous magnesium sulfate. After filtration of solutions to remove the drying agents, the solvents were removed under reduced pressure on a Büchi rotary evaporator.

^1H NMR spectra were recorded on either a Varian Unity 300 or Varian Inova 500 instrument. ^{13}C NMR spectra were recorded on either a Varian XL 300 or a Varian Unity 300 instrument. All chemical shifts are reported relative to residual CHCl_3 (7.26 ppm) for ^1H , and CDCl_3 (77.0 ppm) for ^{13}C NMR spectra.

IR spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer, either as KBr plates or films.

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected.

HRMS were obtained on a Kratos MS80RFA instrument operating in EI mode at 70 eV and 4 kV accelerating potential.

Analytical TLC was conducted on aluminium-backed Merck Kieselgel KG60F254 silica plates or Fluka aluminium-backed alumina type H plates. The developed plates were analysed under short-wave ultraviolet light and stained with a potassium permanganate dip. Unless otherwise stated flash chromatography was performed on Merck Silica 60 following the guidelines given by Still *et al.*¹³⁶ In other cases Laporte Alumina, Grade H, 100-200 mesh was used.

Optical rotations were measured on a Perkin Elmer Polarimeter, Model 341. Samples were prepared in a 5 mL volumetric flask at the stated concentration (g/100 mL) and in the stated spectrophotometric grade solvent. Measurements were taken at 589 nm (sodium D line), and at a temperature of 20 °C in a 1dm pathlength optical cell. Values are quoted as specific rotations calculated according to the following formula (Figure 6.1).

$$[\alpha]_D^t = \frac{100\alpha}{l c}$$

$[\alpha]_D^t$ = specific rotation at t °C
 α = number of degrees
 l = path length in dm
 c = concentration in g/100 mL

Figure 6.1 Formula for calculation of specific rotation.

Values for enantiomeric excess were determined using the method described by Mosher *et al.*¹¹⁸ (*S*)-MTPA-Cl was purchased from Fluka and a stock solution made up by taking a small amount (*ca* 5-10 mg) and dissolving it in 0.5 mL of dry dichloromethane in a vial with a teflon screwcap. The resulting solution was stored under dry nitrogen in the freezer and used as required.

Solvents and reagents were purified according to well established procedures.¹³⁷ In particular *t*-butylamine, dichloromethane, toluene, triethylamine, pyridine, and *N,N*-diisopropylamine were freshly distilled from calcium hydride before use. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone before use. Acetone was dried over 4Å molecular sieves for 24 h, then distilled and stored under dry nitrogen. *N,N*-Dimethylformamide was dried by standing over 4Å molecular sieves for two periods of 24 h, before being stored under dry nitrogen over 4Å molecular sieves. Petroleum ether used had a boiling point of 50-70 °C. *n*-Butyllithium in hexanes was purchased from Acros Organics and titrated with *s*-butanol, using 1,10-phenanthroline as the indicator in a solution of dry diethyl ether.¹³⁸ *p*-Toluenesulfonyl chloride was recrystallised before use and stored under dry nitrogen.¹³⁹ Acetyl chloride was freshly distilled from quinoline (*ca* 10:1) under an atmosphere of dry nitrogen as required. Copper(I) iodide was purified by refluxing with dichloromethane in a Soxhlet apparatus for 24 h. The resulting white powder was stored under dry nitrogen and protected from light. Phenols 2.31 and 2.32 were prepared according to a literature procedure.⁶¹ Triflic anhydride was prepared as described by Stang and Deuber.⁵⁹ 1,1-Diethoxyethylene was prepared as described by McElvain and Kundiger.¹⁴⁰ Benzyltrimethylammonium tribromide was prepared by a

literature procedure.⁶³ Bromoallene was prepared by isomerisation of propargyl bromide.⁷⁰ Propargyl chloride was prepared as a solution in benzene as described by Vernon⁷⁴ and the composition of this solution determined by ¹H NMR analysis. Silver(I) oxide was freshly prepared and stored under an atmosphere of dry nitrogen protected from light.¹⁴¹ PdCl₂(PPh₃)₂¹⁴² and Pd(PPh₃)₄¹⁴³ were prepared according to literature procedures. Pd(PPh₃)₄ was stable for 3-4 months if wrapped in several layers of foil and stored in the freezer. MOM-Cl was prepared by a literature procedure¹⁴⁴ and stored in the freezer. If fuming excessively it was redistilled from a small amount of calcium hydride under an atmosphere of dry nitrogen. 4-Iodo-3,5-dimethoxybenzaldehyde **3.6** was prepared from 2,6-dimethoxyterephthalic acid dimethyl ester¹⁴⁵ as described by Kompis and Wick.⁸⁰ Anhydrous *t*-butylhydroperoxide solutions were prepared as described by Sharpless et al.¹¹⁷

6.2 Notes on Nomenclature

The nomenclature system used in this thesis is in accordance with the IUPAC recommendations¹⁴⁶, with the following exceptions.

The benzocyclobutenones and benzocyclobutenols synthesised in Chapter 2 have been named according to the base structures shown below (Figure 6.2).

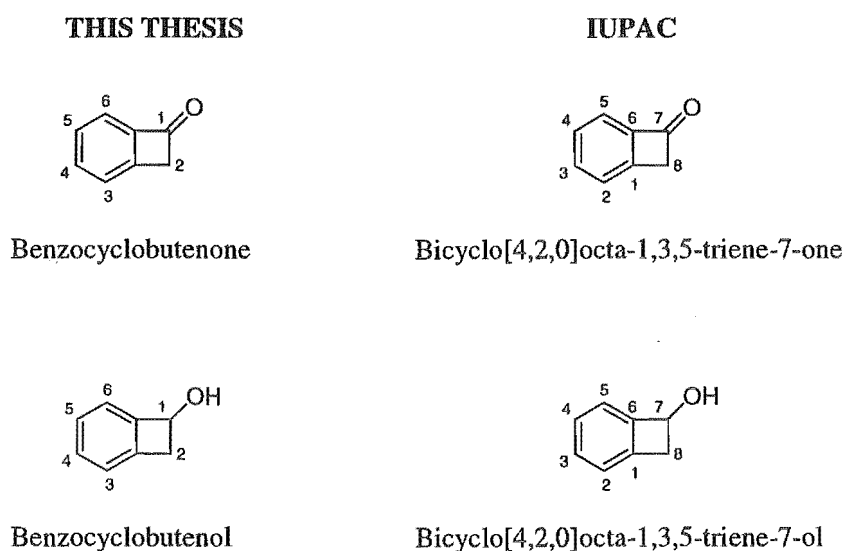
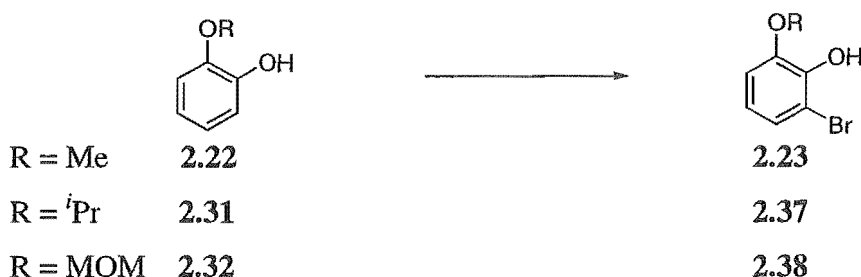


Figure 6.2 Base structures for naming of the benzocyclobutenones and benzocyclobutenols.

6.3 Experiments Described in Chapter 2

General Procedure for the *Ortho*-Bromination of Phenols 2.22, 2.31, and 2.32



Br₂ (1.0 equiv) was added dropwise to a solution of dry *tert*-butylamine (2.0 equiv) in dry toluene (1 M) was cooled to $-30\text{ }^{\circ}\text{C}$ and the resulting solution stirred at this temperature for 30 min. The resulting turbid solution was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of the appropriate phenol 2.22, 2.31, or 2.32 (1.0 equiv) in dry CH₂Cl₂ (6 M) was slowly added. The reaction was allowed to warm to r.t. over a period of 5 h. After this time Et₂O and H₂O were added and the aqueous layer acidified to pH 1 with 1 M HCl solution. The aqueous layer was extracted with a further portion of Et₂O and the combined organic extracts were washed in turn with 1 M HCl solution and 10 % w/v Na₂S₂O₃ solution. After removal of the solvent under reduced pressure, the residue was purified by bulb to bulb distillation.

2-Bromo-6-methoxyphenol 2.23

Yield: 91%.⁵⁷

2-Bromo-6-isopropoxyphenol 2.37

Bp: $113\text{ }^{\circ}\text{C}$ @ 11 mm/Hg.

Yield: 85 %.

¹H NMR (300 MHz, CDCl₃): δ 1.37 [d, $J = 6.4\text{ Hz}$, 6H], 6.04 [br s, 1H], 4.58 [m, 1H], 6.71 [m, 1H], 6.81 [dd, $J = 7.8, 1.5\text{ Hz}$, 1H], 7.07 [dd, $J = 8.3, 1.5\text{ Hz}$, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 21.8, 72.1, 108.0, 112.2, 120.3, 124.6, 143.9, 145.1.

IR (film): 3508 cm^{-1} .

HRMS: Calcd for $C_9H_{11}^{79}BrO_2$ (M^+) 229.9943, found 229.9940.

2-Bromo-6-methoxymethoxyphenol 2.38

Bp: 135 °C @ 11 mm/Hg.

Yield: 80 %.

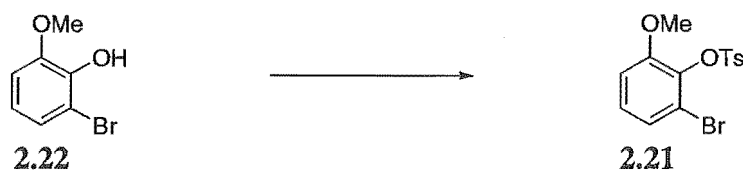
1H NMR (300 MHz, $CDCl_3$): δ 3.52 [s, 1H], 5.21 [s, 2H], 6.25 [br s, 1H], 6.72 [t, J = 8.3 Hz, 1H], 7.05 [m, 1H], 7.16 [m, 1H].

^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3, 95.7, 108.8, 114.6, 120.6, 126.2, 143.7, 144.9.

IR (film): 3501 cm^{-1} .

HRMS: Calcd for $C_8H_9^{79}BrO_3$ (M^+) 231.9735, found 231.9733.

Toluene-4-sulfonic acid 2-bromo-6-methoxyphenyl ester 2.21



p-Toluenesulfonyl chloride (0.940 g, 4.93 mmol) was added in portions over 20 min to a stirred solution of the phenol **2.22** (1.00 g, 4.93 mmol) and dry NEt_3 (1.03 mL, 7.41 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. The solution was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (25 mL), and washed in turn with water, then sat aq $NaHCO_3$ solution. The solvent was removed under reduced pressure to give the title compound as a white solid (1.75 g, 99 %).

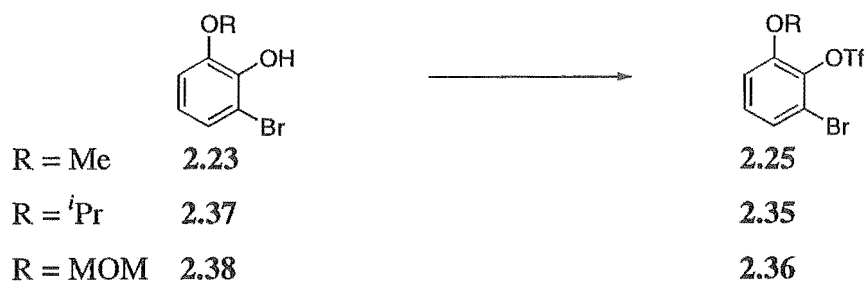
Mp: 81-82 °C.

1H NMR (300 MHz, $CDCl_3$): δ 2.47 [s, 3H], 3.65 [s, 3H], 6.86 [dd, J = 8.3, 1.5 Hz, 1H], 7.07 [dd, J = 8.3, 7.8 Hz, 1H], 7.15 [dd, J = 7.8, 1.5 Hz, 1H], 7.35 [d, J = 8.3 Hz, 2H], 7.89 [d, J = 8.3 Hz, 2H].

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 55.8, 111.6, 118.2, 124.8, 128.1, 128.2, 129.3, 134.7, 137.3, 144.9, 153.5.

HRMS: Calcd for $C_{14}H_{13}^{79}BrO_4^{32}S$ (M^+) 355.9718, found 355.9718.

General Procedure for the Preparation of Triflates 2.25, 2.35, and 2.36;



Triflic anhydride (1.5 equiv) was added dropwise *via* syringe to a solution of phenol **2.23**, **2.37**, or **2.38** (1.0 equiv) in dry pyridine (2.0 M) at 0 °C. The reaction was stirred at this temperature for 5 min, then allowed to warm to r.t. overnight. The resulting solution was poured into H₂O and extracted with Et₂O (4 x 20 mL). The combined organic extracts were washed in turn with 10 % (v/v) HCl solution and H₂O. The solvent was removed under reduced pressure to afford an oil, which was purified by bulb to bulb distillation.

Trifluoromethanesulfonic acid 2-bromo-6-methoxyphenyl ester **2.25**

Yield: 98%.

Bp: 95 °C @ 3 mm/Hg.

¹H NMR (300 MHz, CDCl₃): δ 3.92 [s, 3H], 6.98 [dd, *J* = 7.8, 2.0 Hz, 1H], 7.18 [dd, *J* = 8.3, 7.8 Hz, 1H], 7.23 [dd, *J* = 8.3, 2.0 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 56.3, 112.0, 116.5, 118.6 [q, *J*_{C-F} = 321 Hz], 125.1, 129.3, 136.9, 152.6.

HRMS: Calcd for C₈H₆⁷⁹BrF₃O₄³²S (M⁺) 333.9123, found 333.9122.

Trifluoromethanesulfonic acid 2-bromo-6-isopropoxyphenyl ester **2.35**

Yield: 88%.

Bp: 130 °C @ 11 mm/Hg.

¹H NMR (300 MHz, CDCl₃): δ 1.39 [d, *J* = 6.0 Hz, 6H], 4.69 [m, 1H], 6.95 [m, 1H], 7.11-7.19 [m, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 21.3, 72.2, 113.5, 116.6, 118.5 ($J_{\text{C-F}} = 321$ Hz), 129.1, 124.5, 137.5, 150.9.

HRMS: Calcd for $\text{C}_{10}\text{H}_{10}^{79}\text{BrF}_3^{32}\text{SO}_4$ (M^+) 361.9436, found 361.9433.

Trifluoromethanesulfonic acid 2-bromo-6-methoxymethoxyphenyl ester **2.36**

Yield: 89 %.

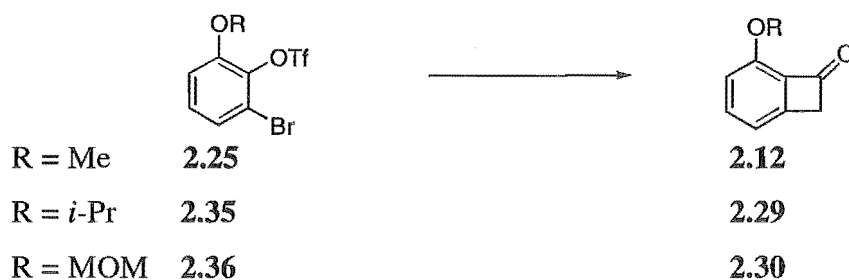
Bp: 135 °C @ 11 mm/Hg.

^1H NMR (300 MHz, CDCl_3): δ 3.52 [s, 3H], 5.25 [s, 2H], 7.15 [dd, $J = 8.3, 7.8$ Hz, 1H], 7.24-7.29 [m, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 56.6, 95.3, 115.2, 116.4, 118.5 ($J_{\text{C-F}} = 321$ Hz), 126.2, 129.3, 137.3, 150.4.

HRMS: Calcd for $\text{C}_9\text{H}_8^{79}\text{BrF}_3^{32}\text{SO}_5$ (M^+) 363.9228, found 363.9226.

General procedure for the Preparation of 6-Alkoxybenzocyclobutenones **2.12**, **2.29**, and **2.30**



A stirred solution of triflate **2.25**, **2.35**, or **2.36** (1.0 equiv) and 1,1-diethoxyethylene **2.14** (2.0 equiv) in dry THF (0.2 M) was cooled to -95 °C. A solution of *n*-BuLi in hexanes (1.74 M, 2.0 equiv) was added dropwise via syringe and the resulting mixture stirred at -95 °C for 30 min, then allowed to warm to r.t. overnight. The resulting acetal was hydrolysed *in situ* by addition of aq H_2SO_4 solution (3 % v/v, 0.83 M), followed by vigorous stirring at r.t. for 3h. The resulting solution was poured into H_2O , and extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed in turn with sat aq NaHCO_3 solution and H_2O . The solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography on silica gel using the solvents indicated.

6-Methoxybenzocyclobuten-1-one 2.12

Chromatography: 10 % EtOAc/petroleum ether.

Yield: white solid; 72 %.

Mp: 34-35 °C Lit (32-33 °C).¹⁴⁷

¹H NMR (300 MHz, CDCl₃): δ 3.93 [s, 2H], 4.12 [s, 3H], 6.80 [d, *J* = 8.3 Hz, 1H], 7.03 [d, *J* = 6.8 Hz, 1H], 7.43 [dd, *J* = 8.3, 6.8 Hz, 1H].

6-Isopropoxybenzocyclobuten-1-one 2.29

Bp: 80 °C @ 11 mm/Hg.

Chromatography: 5 % ether/petroleum.

Yield: white solid; 62%.

Mp: 34-35 °C.

¹H NMR (300 MHz, CDCl₃): δ 1.34 [d, *J* = 5.9 Hz, 6H], 3.89 [s, 2H], 5.09 [m, 1H], 6.77 [d, *J* = 8.3 Hz, 1H], 6.97 [d, *J* = 7.3 Hz, 1H], 7.41 [dd, *J* = 8.3, 7.3 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 22.0, 50.7, 74.4, 114.2, 116.7, 131.7, 137.6, 150.3, 151.8, 184.7.

IR (KBr): 1765 cm⁻¹.

HRMS: Calcd for C₁₁H₁₂O₂ (M⁺) 176.0837, found 176.0837.

6-Methoxymethoxybenzocyclobuten-1-one 2.30

Chromatography: 5 % ether/petroleum ether.

Yield: white solid; 55 %.

Mp: 37-40 °C.

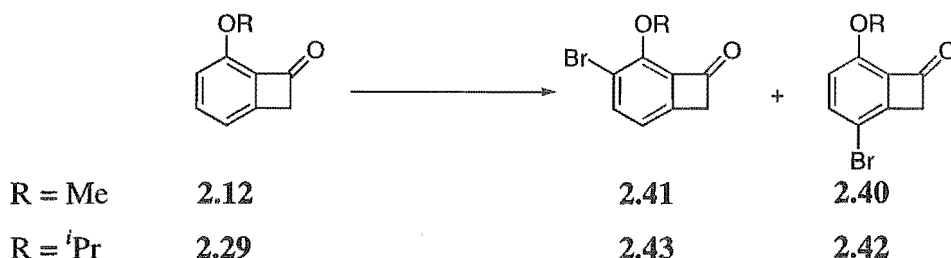
¹H NMR (300 MHz, CDCl₃): δ 3.48 [s, 3H], 3.92 [s, 2H], 5.48 [s, 2H], 6.89 [d, *J* = 8.3 Hz, 1H], 7.08 [d, *J* = 7.3 Hz, 1H], 7.46 [dd, *J* = 8.3, 7.3 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 51.1, 56.6, 96.2, 115.8, 116.4, 132.8, 137.7, 149.4, 150.5, 184.6.

IR (KBr): 1761 cm⁻¹.

HRMS: Calcd for C₁₀H₁₀O₃ (M⁺) 178.0630, found 178.0630.

General Procedure for the Bromination of 6-Alkoxybenzocyclobutenones **2.12** and **2.29**



Benzyltrimethylammonium tribromide (1.1 equiv) and ZnCl_2 (1.2 equiv) were added to a stirred solution of benzocyclobutenone **2.12** or **2.29** (1.0 equiv) in acetic acid (0.25 M). The reaction was stirred at r.t. for 24 h, followed by addition of water (20 mL) and 5 % w/v NaHSO_3 solution (10 mL). The crude product was extracted with ethyl acetate (4 x 40 mL) and the combined organic extracts washed with water. Removal of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel using the solvents indicated.

Bromination of 6-methoxybenzocyclobuten-1-one **2.12**

Chromatography: 10 % EtOAc/petroleum ether gave in order of elution;

(i) 3-Bromo-6-methoxybenzocyclobuten-1-one **2.40**

Yield: white solid; 82 %

Mp: 74-75 °C Lit (75 °C)¹⁴⁸

¹H NMR (300 MHz, CDCl_3): δ 3.89 [s, 2H], 4.09 [s, 3H], 6.71 [d, J = 8.8 Hz, 1H], 7.46 [d, J = 8.8 Hz, 1H];

(ii) 5-Bromo-6-methoxybenzocyclobuten-1-one **2.41**

Yield: white solid; 9 %

Mp: 119-120 °C.

^1H NMR (300 MHz, CDCl_3): δ 3.89 [s, 2H], 4.24 [s, 3H], 6.93 [d, $J = 7.3$ Hz, 1H], 7.67 [d, $J = 7.8$ Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 50.6, 60.7, 109.9, 116.1, 132.7, 140.4, 149.5, 149.8, 182.9,.

IR (KBr): 1774 cm^{-1} .

HRMS: Calcd for $\text{C}_9\text{H}_7^{79}\text{BrO}_2$ (M^+) 225.9630, found 225.9629.

Bromination of 6-isopropoxybenzocyclobuten-1-one 2.29

Chromatography: 5 % EtOAc/petroleum ether gave in order of elution;

(i) 3-Bromo-6-isopropoxybenzocyclobuten-1-one 2.42

Yield: white solid; 80 %.

Mp: 81-82 °C.

^1H NMR (300 MHz, CDCl_3): δ 1.33 [d, $J = 5.9$ Hz, 6H], 3.86 [s, 2H], 5.01 [m, 1H], 6.68 [d, $J = 8.8$ Hz, 1H], 7.46 [d, $J = 8.8$ Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 22.0, 51.2, 75.2, 105.3, 119.6, 132.2, 140.1, 149.9, 151.4, 182.1.

IR (KBr): 1762 cm^{-1} .

HRMS: Calcd for $\text{C}_{11}\text{H}_{11}^{79}\text{BrO}_2$ (M^+) 253.9943, found 253.9940;

(ii) 5-Bromo-6-isopropoxybenzocyclobuten-1-one 2.43

Yield: colourless oil; 12%.

^1H NMR (300 MHz, CDCl_3): δ 1.39 [d, $J = 6.4$ Hz, 6H], 3.86 [s, 2H], 5.21 [m, 1H], 6.88 [d, $J = 7.3$ Hz, 1H], 7.67 [d, $J = 7.3$ Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 22.1, 50.4, 75.9, 110.9, 115.4, 132.3, 140.7, 148.6, 149.5, 183.3,.

IR (film): 1768 cm^{-1} .

HRMS: Calcd for $\text{C}_{11}\text{H}_{11}^{79}\text{BrO}_2$ (M^+) 253.9943, found 253.9940.

1-Ethynyl-6-methoxybenzocyclobuten-1-ol 2.45

A solution of ethynylmagnesium bromide in THF (0.5 M, 2.11 mL, 1.05 mmol) was added dropwise to a stirred solution of 6-methoxybenzocyclobuten-1-one **2.12** (0.142 g, 0.958 mmol) in dry toluene (10 mL) at 0 °C. The reaction was warmed to 10 °C, then stirred for 2 h, while allowing to warm to room temperature. The solution was cooled to -50 °C and saturated aqueous NH₄Cl solution (15 mL) was added dropwise. The mixture was allowed to warm to r.t. and the organic layer separated. The aqueous layer was acidified to pH 1 with 10 % v/v HCl solution and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with 1 % v/v HCl solution. Removal of the solvent under reduced pressure gave an oily residue, which was purified by silica gel flash chromatography, eluting with 20 % ethyl acetate/petroleum ether, to give the title compound as a white solid (0.112 g, 67 %).

Mp: 77-78 °C.

¹H NMR (300 MHz, CDCl₃): δ 2.83 [s, 1H], 2.66 [s, 1H], 3.43 [d, *J* = 14 Hz, 1H], 3.76 [d, *J* = 14 Hz, 1H], 4.07 [s, 3H], 6.75 [m, 2H], 7.25 [dd, *J* = 8.4, 7.2 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 49.5, 57.3, 70.1, 72.9, 84.9, 114.4, 115.9, 130.4, 131.8, 143.1, 153.1.

IR (KBr): 3252 cm⁻¹.

HRMS: Calcd for C₁₁H₁₀O₂ (M⁺) 174.0681, found 174.0681.

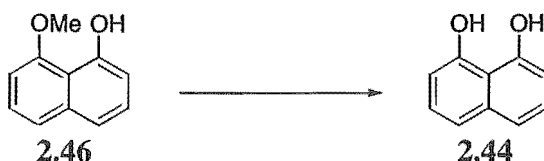
8-Methoxynaphthalen-1-ol 2.46

A solution of the acetylene **2.45** (85 mg, 0.49 mmol) in dry toluene (7 mL) was heated at reflux for 36 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 10 % EtOAc/petroleum ether, to give the title compound as a white solid (51 mg, 60 %).

Mp: 45-46 °C Lit (45-46 °C)¹⁴⁹ (55-56 °C).¹⁵⁰

¹H NMR (300 MHz, CDCl₃) δ 4.05 [s, 3H], 6.78 [d, *J* = 7.3 Hz, 1H], 6.89 [dd, *J* = 7.3, 1.5 Hz, 1H], 7.28-7.39 [m, 3H], 7.42 [dd, *J* = 8.3, 0.98 Hz, 1H], 9.34 [s, 1H].

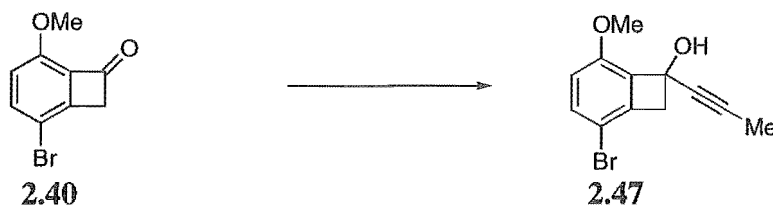
Naphthalene-1,8-diol **2.44**



A solution of boron tribromide (1.0 M, 3.50 mmol) in dry CH₂Cl₂ (3.5 mL) was added dropwise to a solution of the methyl ether **2.46** (0.559 g, 3.21 mmol) in dry CH₂Cl₂ at - 78 °C. The resulting solution was allowed to warm slowly to r.t. overnight, followed by addition of H₂O (20 mL). The aqueous layer was acidified to pH 1 with 10 % v/v HCl solution, then extracted with EtOAc (x4). The combined organic extracts were washed with 10 % HCl solution and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel, eluting with 50 % EtOAc/petroleum ether, gave the title compound as a white solid (0.399 g, 78 %).

Mp: 130-140 °C (Lit 140 °C).⁶⁴

¹H NMR (300 MHz, CDCl₃): δ 8.03 [s, 1H], 7.37 [dd, *J* = 8.3, 0.98 Hz, 1H], 7.29 [dd, *J* = 7.3, 8.3 Hz, 1H], 6.80 [dd, *J* = 7.3, 0.98 Hz, 1H].

3-Bromo-6-methoxy-1-propynylbenzocyclobuten-1-ol 2.47

A solution of dry diisopropylamine (2.80 mL, 20.0 mmol) in dry THF (20 mL) was cooled to 0 °C. A solution of *n*-BuLi in hexanes (1.63 M, 12.27 mL, 20.0 mmol) was added dropwise and the resulting mixture stirred at 0 °C for 15 min. This solution was cooled to -60 °C and 1,2-dibromopropane (0.695 mL, 6.67 mmol) was added dropwise. The reaction was stirred for 20 min at 0 °C and the resulting cloudy solution was re-cooled to -60 °C. A pre-cooled (-60 °C) solution of the ketone **2.40** (0.757 g, 3.33 mmol) in dry THF (30 mL) was slowly added. The reaction was maintained at -60 °C for 2 h, followed by dropwise addition of satd aq NH₄Cl solution. EtOAc (50 mL) was added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with three further portions of EtOAc and the solvents removed under reduced pressure. Purification of the residue by flash chromatography, eluting with 30 % EtOAc/petroleum ether, gave the title compound as a white solid (0.643 g, 72%).

Mp: 95-96 °C.

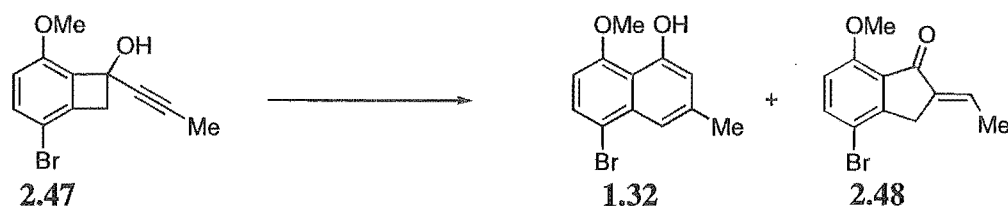
¹H NMR (300 MHz, CDCl₃): δ 1.86 [s, 1H], 3.00 [s, 1H], 3.31 [d, *J* = 14 Hz, 1H], 3.60 [d, *J* = 14 Hz, 1H], 4.04 [s, 3H], 6.62 [d, *J* = 8.8 Hz, 1H], 7.26 [d, *J* = 8.8 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 3.6, 49.6, 57.7, 69.2, 80.0, 81.7, 106.7, 117.1, 132.4, 133.6, 142.7, 152.6.

IR (KBr): 2240, 3157 cm⁻¹.

HRMS: Calcd for C₁₂H₁₁⁷⁹BrO₂ (M⁺) 265.9943, found 265.9942.

(E)-4-Bromo-2-ethylidene-7-methoxyindan-1-one 2.48 and 5-bromo-8-methoxy-3-methylnaphthalen-1-ol 1.32



A solution of the acetylene **2.47** (148 mg) in dry toluene (8 mL) was heated at reflux for 18 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, as detailed below.

Chromatography: 30 % EtOAc/petroleum ether.

4-Bromo-2-ethylidene-7-methoxyindan-1-one 2.48

Yield: cloudy oil; (40 mg, 27 %).

¹H NMR (300 MHz, CDCl₃): δ 1.96 [m, 3H], 3.51 [m, 2H], 3.94 [s, 3H], 6.74 [d, *J* = 8.8 Hz, 1H], 6.90 [m, 1H], 7.62 [d, *J* = 8.8 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 15.2, 31.1, 56.0, 111.3, 111.4, 128.5, 132.9, 136.7, 138.1, 150.9, 157.8, 190.4.

IR (film): 1705 cm⁻¹.

HRMS: Calcd for C₁₂H₁₁⁷⁹BrO₂ (M⁺) 265.9943, found 265.9942.

The remaining fractions from this column were pooled and further purified:

Chromatography: 20 % acetone/petroleum ether.

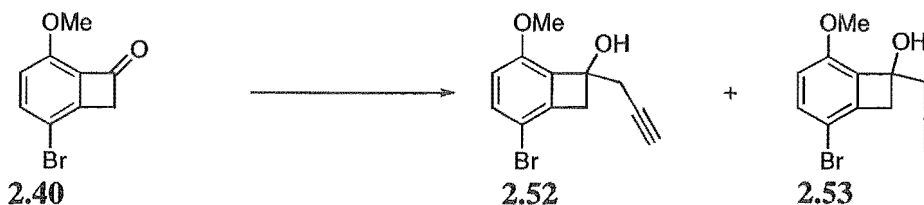
5-Bromo-8-methoxy-3-methylnaphthalen-1-ol 1.32

Yield: white solid; (30 mg, 20 %).

Mp: 104-105 °C Lit (100-102 °C).¹⁵¹

^1H NMR (300 MHz, CDCl_3): δ 2.48 [s, 3H], 3.99 [s, 3H], 6.51 [d, $J = 8.3$ Hz, 1H], 6.81 [d, $J = 1.5$ Hz, 1H], 7.47 [d, $J = 0.98$ Hz, 1H], 7.54 [d, $J = 8.3$ Hz, 1H], 9.32 [s, 1H].

Addition of Allenyllithium to Benzocyclobutenone **2.40**



A solution of *n*-BuLi in hexanes (1.5 M, 300 μL , 0.471 mmol) was added to a solution of bromoallene in dry Et_2O (0.5 mL) at -78°C . The reaction was stirred for 25 min at this temperature then a solution of benzocyclobutenone **2.40** (74 mg, 0.315 mmol) in dry THF (0.5 mL) was added dropwise. The reaction was stirred at -78°C for 1 h, followed by addition of sat aq NH_4Cl solution at this temperature. The solution was warmed to r.t. and extracted with EtOAc (x 4). The solvent was removed under reduced pressure to give a residue which was purified by flash chromatography on silica gel, eluting with 30 % EtOAc /petroleum ether, to give the title a 95:5 mixture of **2.52**:**2.53**, as determined by ^1H NMR spectroscopy, in 92 % yield.

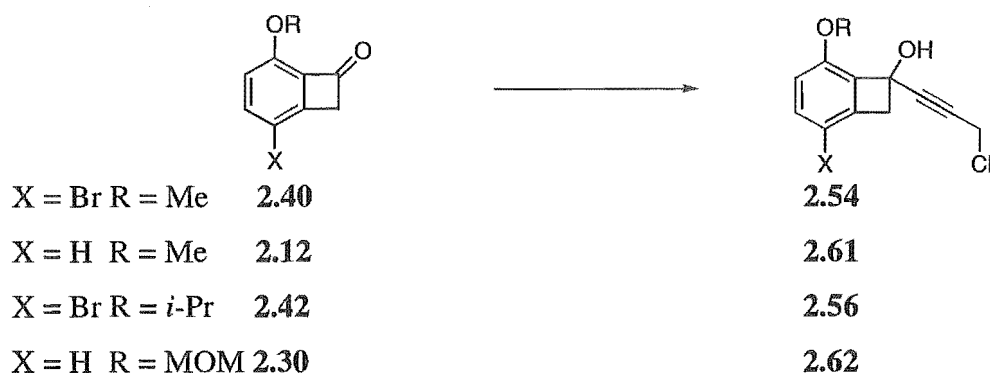
3-Bromo-6-methoxy-1-prop-2-ynylbenzocyclobuten-1-ol **2.52**

^1H NMR (300 MHz, CDCl_3): δ 2.06 [m, 1H], 2.69 [dd, $J = 17, 2.4$ Hz, 1H], 2.95 [m, 2H], 3.13 [d, $J = 14$ Hz, 1H], 3.39 [d, $J = 14$ Hz, 1H], 3.84 [s, 3H], 6.60 [d, $J = 8.8$ Hz, 1H], 7.27 [d, $J = 8.8$ Hz, 1H].

3-Bromo-6-methoxy-1-propadienylbenzocyclobuten-1-ol **2.53**

^1H NMR (300 MHz, CDCl_3): δ 3.25 [d, $J = 14$ Hz, 1H], 3.43 [d, $J = 14$ Hz, 1H], 3.89 [s, 3H], 5.00 [m, 2H], 5.64 [dd, $J = 6.4, 6.8$ Hz, 1H], 6.61 [d, $J = 8.8$ Hz, 1H], 7.26 [d, $J = 8.8$ Hz, 1H].

General Procedure for the Addition of Lithiopropargylchloride to 6-Alkoxybenzocyclobutenones 2.12, 2.30, 2.40, and 2.42



A solution of *n*-BuLi in hexanes (1.55 M, 2 equiv) was added dropwise to a solution of propargyl chloride in benzene (43 wt % solution, 2.0 equiv) and dry ether (1 M) at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min. A pre-cooled ($-78\text{ }^{\circ}\text{C}$) solution of benzocyclobutenone **2.40**, **2.12**, **2.42**, or **2.30** (1 equiv) in dry THF (0.2 M) was added dropwise *via* cannula. The reaction was allowed to warm slowly to $-60\text{ }^{\circ}\text{C}$ over 1 h, and maintained at this temperature for a further 3 h. After this time the reaction was cooled to $-78\text{ }^{\circ}\text{C}$ and water (30 mL) was slowly added. The mixture was allowed to warm to room temperature and extracted with ethyl acetate (x 4). The cloudy solution was washed with brine, dried over anhydrous MgSO_4 , then filtered through a plug of silica gel (**CAUTION!!**: Residues from this procedure should be disposed of immediately as if left to dry they have been known to ignite upon contact). Removal of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel using the solvents indicated.

3-Bromo-1-(3-chloropropynyl)-6-methoxybenzocyclobuten-1-ol **2.54**

Chromatography: 20 % EtOAc/petroleum ether.

Yield: pale yellow viscous oil; 95%.

^1H NMR (300 MHz, CDCl_3): δ 3.34 [d, $J = 14\text{ Hz}$, 1H], 3.65 [d, $J = 14\text{ Hz}$, 1H], 4.03 [s, 3H], 4.18 [s, 2H], 6.64 [d, $J = 9.3\text{ Hz}$, 1H], 7.29 [d, $J = 8.8\text{ Hz}$, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 30.1, 49.1, 57.5, 68.6, 79.8, 86.5, 106.7, 117.1, 131.3, 134.0, 142.4, 152.5.

IR (film): 3375 cm^{-1} .

HRMS: Calcd for $\text{C}_{12}\text{H}_{10}^{79}\text{Br}^{35}\text{ClO}_2$ (M^+) 299.9553, found 299.9553.

1-(3-Chloropropynyl)-6-methoxybenzocyclobuten-1-ol 2.61

Chromatography: 20 % EtOAc/petroleum ether.

Yield: colourless viscous oil; 76%.

^1H NMR (300 MHz, CDCl_3): δ 2.91 [br s, 1H], 3.43 [d, $J = 13.7$ Hz, 1H], 3.74 [d, $J = 14.2$ Hz, 1H], 4.06 [s, 3H], 4.19 [s, 2H], 6.74 [d, $J = 8.3$ Hz, 1H], 6.75 [d, $J = 7.3$ Hz, 1H], 7.25 [dd, $J = 8.3, 7.3$ Hz].

^{13}C NMR (75 MHz, CDCl_3): δ 30.3, 49.5, 57.2, 70.1, 79.3, 87.4, 114.4, 115.9, 130.3, 131.8, 143.0, 153.0.

IR (film): 3383 cm^{-1} .

HRMS: Calcd for $\text{C}_{12}\text{H}_{11}^{35}\text{ClO}_2$ (M^+) 222.0448, found 222.0448.

3-Bromo-1-(3-chloropropynyl)-6-isopropoxybenzocyclobuten-1-ol 2.56

Chromatography: 20 % EtOAc/petroleum ether.

Yield: viscous brown oil; 84%.

^1H NMR (300 MHz, CDCl_3): δ 1.35 [m, 6H], 2.92 [br s, 1H], 3.34 [d, $J = 14$ Hz, 1H], 3.63 [d, $J = 14$ Hz, 1H], 4.18 [s, 2H], 4.82 [m, 1H], 6.64 [d, $J = 9.3$ Hz, 1H], 7.28 [d, $J = 9.3$ Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 22.3, 22.7, 30.0, 49.0, 68.9, 72.7, 79.4, 85.8, 106.6, 118.7, 132.1, 134.0, 142.5, 150.9.

IR (film): 3396 cm^{-1} .

HRMS: Calcd for $\text{C}_{14}\text{H}_{14}^{79}\text{Br}^{35}\text{ClO}_2$ (M^+) 327.9866, found 327.9863.

1-(3-Chloropropynyl)-6-methoxymethyloxybenzocyclobuten-1-ol 2.62

Chromatography: 20 % EtOAc/petroleum ether.

Yield: pale yellow viscous oil; 60 %.

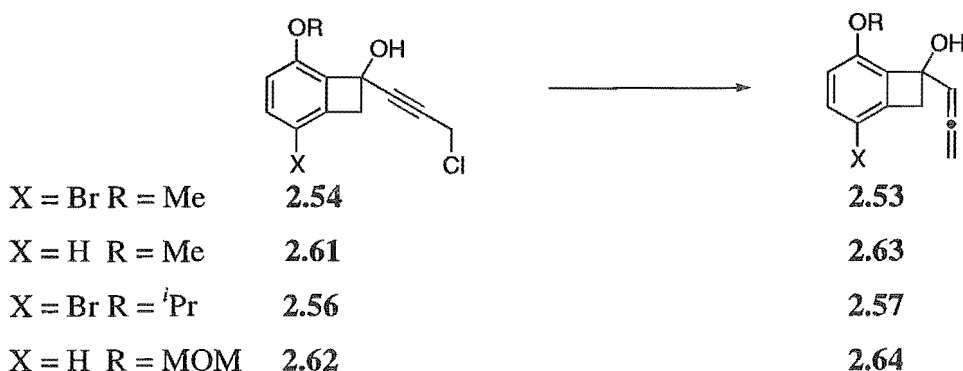
^1H NMR (300 MHz, CDCl_3): δ 3.44 [d, $J = 14$ Hz, 1H], 3.56 [s, 3H], 3.63 [d, $J = 14$ Hz, 1H], 4.18 [m, 1H], 5.00 [d, $J = 7.3$ Hz, 1H], 5.82 [d, $J = 7.3$ Hz, 1H], 6.82 [m, 2H], 7.25 [m, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 30.4, 47.4, 56.3, 69.7, 78.9, 88.7, 94.5, 116.5, 117.4, 130.8, 131.5, 143.5, 148.6.

IR (film): 3423 cm^{-1} .

HRMS: Calcd for $\text{C}_{13}\text{H}_{13}^{35}\text{ClO}_3$ (M^+) 252.0553, found 252.0553.

General Procedure for the Reduction of Acetylenes 2.54, 2.56, 2.61, and 2.62



A solution of acetylene **2.54**, **2.61**, **2.56**, or **2.62** (1.0 equiv) in dry THF (0.1 M) was added dropwise to a suspension of LiAlH_4 (2.0 equiv) in dry THF (0.2 M), at $0\text{ }^\circ\text{C}$. The resulting solution was allowed to warm to r.t. and stirred for 30 min. The reaction was cooled to $0\text{ }^\circ\text{C}$ and quenched *via* dropwise addition of 1 M HCl solution. Water was added and the product extracted with ethyl acetate (x 4). The solvent was removed under reduced pressure to give the allenes, which were of sufficient purity for the next reaction.

3-Bromo-6-methoxy-1-propadienylbenzocyclobuten-1-ol **2.53**

Yield: pale yellow viscous oil; 95 %.

^1H NMR (300 MHz, CDCl_3): δ 3.25 [d, $J = 14\text{ Hz}$, 1H], 3.43 [d, $J = 14\text{ Hz}$, 1H], 3.89 [s, 3H], 5.00 [m, 2H], 5.64 [dd, $J = 6.4, 6.8\text{ Hz}$, 1H], 6.61 [d, $J = 8.8\text{ Hz}$, 1H], 7.26 [d, $J = 8.8\text{ Hz}$, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 47.0, 57.1, 75.3, 79.3, 96.2, 106.8, 116.2, 133.2, 133.6, 142.2, 153.1, 205.8.

IR (film): $1956, 3383\text{ cm}^{-1}$.

HRMS: Calcd for $\text{C}_{12}\text{H}_{11}^{79}\text{BrO}_2$ (M^+) 265.9943, found 265.9942.

6-Methoxy 1-propadienylbenzocyclobuten-1-ol 2.63

Yield: pale yellow oil; 91 %.

¹H NMR (300 MHz, CDCl₃): δ 3.34 [d, *J* = 14 Hz, 1H], 3.52 [d, *J* = 14 Hz, 1H], 3.92 [s, 3H], 4.99 [m, 2H], 5.68 [dd, *J* = 6.8, 6.4 Hz, 1H], 6.73 [m, 2H], 7.23 [m, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 47.4, 56.8, 76.5, 79.2, 96.9, 113.5, 115.8, 131.1, 132.5, 142.7, 153.6, 205.8.

IR (film): 1956, 3404 cm⁻¹.

HRMS: Calcd for C₁₂H₁₂O₂ (M⁺) 188.0837, found 188.0837.

3-Bromo-6-isopropoxy-1-propadienylbenzocyclobuten-1-ol 2.57

Yield: viscous brown oil; 99 %.

¹H NMR (300 MHz, CDCl₃): δ 1.28 [d, *J* = 5.9 Hz], 1.31 [d, *J* = 5.9 Hz], 2.80 [br s, 1H], 3.24 [d, *J* = 14 Hz, 1H], 3.41 [d, *J* = 14 Hz, 1H], 4.66 [m, 1H], 5.00 [m, 2H], 5.60 [dd, *J* = 6.4, 6.8 Hz, 1H], 6.60 [d, *J* = 8.8 Hz, 1H], 7.25 [d, *J* = 8.8 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 22.1, 22.5, 47.0, 72.0, 75.5, 79.5, 95.6, 106.7, 117.9, 133.4, 134.4, 142.4, 151.6, 206.1.

IR (film): 1958, 3400 cm⁻¹.

HRMS: Calcd for C₁₄H₁₅⁷⁹BrO₂ (M⁺) 294.0256, found 294.0253.

6-Methoxymethyloxy-1-propadienylbenzocyclobuten-1-ol 2.64

Yield: viscous pale brown oil; 97 %.

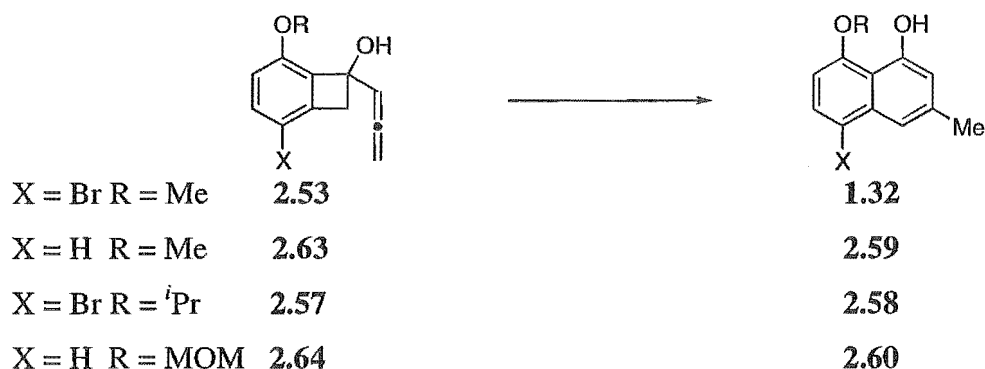
¹H NMR (300 MHz, CDCl₃): δ 3.39 [m, 2H], 3.51 [s, 3H], 4.75 [br s, 1H], 4.92 [m, 2H], 4.97 [d, *J* = 6.8 Hz, 1H], 5.54 [d, *J* = 6.8 Hz, 1H], 5.67 [dd, *J* = 6.4, 6.8 Hz, 1H], 6.80 [m, 2H], 7.23 [dd, *J* = 8.3, 7.3 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 46.4, 56.0, 76.5, 78.6, 94.1, 98.0, 115.9, 117.1, 130.9, 132.5, 143.0, 149.5, 205.7.

IR (film): 1956, 3425 cm⁻¹.

HRMS: Calcd for C₁₃H₁₄O₃ (M⁺) 218.0943, found 218.0943.

General Procedure for the Thermolysis of Allenic Alcohols 2.53, 2.63, 2.57, and 2.64



A solution of the allenic alcohol **2.53**, **2.63**, **2.57**, or **2.64** in dry toluene (0.1 M) was heated at reflux for 4 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel using the solvents indicated.

5-Bromo-8-methoxy-3-methylnaphthalen-1-ol **1.32**

Chromatography: 15 % EtOAc/petroleum ether.

Yield: white solid; 84 %.

Mp: 104-105 °C Lit (105-106 °C).¹⁵¹

¹H NMR (300 MHz, CDCl₃): δ 2.48 [s, 3H], 3.99 [s, 3H], 6.51 [d, *J* = 8.3 Hz, 1H], 6.81 [d, *J* = 1.5 Hz, 1H], 7.47 [d, *J* = 0.98 Hz, 1H], 7.54 [d, *J* = 8.3 Hz, 1H], 9.32 [s, 1H].

8-Methoxy-3-methylnaphthalen-1-ol **2.59**

Chromatography: 15 % EtOAc/petroleum ether.

Yield: white solid; 80 %.

Mp: 93-94 °C, Lit (92-94 °C).¹⁵¹

¹H NMR (300 MHz, CDCl₃): δ 2.42 [s, 3H], 4.04 [s, 3H], 6.70 [dd, *J* = 7.3, 0.98 Hz, 1H], 6.73 [d, *J* = 1.5 Hz, 1H], 7.09 [br s, 1H], 7.26 [m, 1H], 7.32 [dd, *J* = 8.3, 1.5 Hz, 1H], 9.23 [s, 1H].

5-Bromo-8-isopropoxy-3-methylnaphthalen-1-ol 2.58

Chromatography: 5 % EtOAc/petroleum ether.

Yield: white solid 76 %.

Mp: 118-119 °C.

¹H NMR (300 MHz, CDCl₃): δ 1.49 [d, *J* = 6.4 Hz, 6H], 2.47 [s, 3H], 4.81 [m, 1H], 6.60 [d, *J* = 8.3 Hz, 1H], 6.78 [d, *J* = 1.5 Hz, 1H], 7.47 [d, *J* = 0.98 Hz, 1H], 7.56 [d, *J* = 8.3, Hz, 1H], 9.78 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 21.8, 21.9, 73.0, 105.9, 113.0, 114.0, 114.9, 117.7, 129.4, 134.5, 139.3, 153.9, 154.8,.

IR (KBr): 3360 cm⁻¹.

HRMS: Calcd for C₁₄H₁₅⁷⁹BrO₂ (M⁺) 294.0256, found 294.0253.

8-Methoxymethoxy-3-methylnaphthalen-1-ol 2.60

Chromatography: 10 % EtOAc/petroleum ether.

Yield: white solid; 79 %.

Mp: 48-49 °C, Lit (58 °C).¹⁷

¹H NMR (300 MHz, CDCl₃): δ 2.44 [s, 3H], 3.58 [s, 3H], 5.43 [s, 2H], 6.76 [d, *J* = 0.98 Hz, 1H], 6.97 [d, *J* = 7.3 Hz, 1H], 7.11 [s, 1H], 7.26 [m, 1H], 7.38 [d, *J* = 8.3, Hz, 1H], 9.21 [s, 1H].

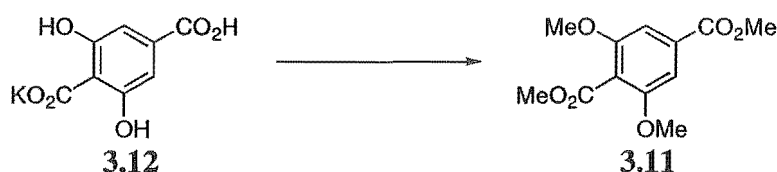
¹³C NMR (75 MHz, CDCl₃): δ 21.4, 56.5, 95.3, 106.6, 112.2, 113.3, 118.3, 121.9, 125.6, 136.8, 137.5, 153.4, 153.7.

IR (KBr): 3416 cm⁻¹.

HRMS: Calcd for C₁₃H₁₄O₃ (M⁺) 218.0943, found 218.0943.

6.4 Experiments Described in Chapter 3

2,6-Dimethoxyterephthalic acid dimethyl ester 3.11

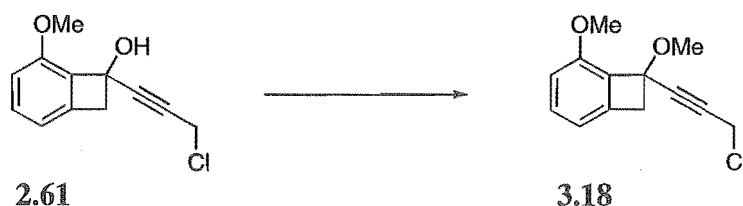


A solution of the acid **3.12** (7.88 g, 33.4 mmol) in dry DMF (150 mL) was added to a suspension of prewashed NaH (4.82 g, 200 mmol) in dry DMF (70 mL) at 0 °C. The reaction was stirred for 5 min at 0 °C, followed 30 min at r.t., then recooled to 0 °C. Iodomethane (25 mL) was slowly added and the reaction was allowed to warm slowly to r.t. overnight. The reaction was carefully quenched by addition of H₂O (200 mL), then diluted with 1 M HCl solution (200 mL). The aqueous phase was extracted with EtOAc (x 4) and the combined organic extracts were washed with 5 % w/v Na₂S₂O₃ solution. Removal of the solvent under reduced pressure gave the title compound as a white solid (8.55 g, 100 %).

¹H NMR (500 MHz, CDCl₃): δ 3.87 [s, 6H], 3.92 [s, 3H], 3.93 [s, 3H], 7.24 [s, 2H].

Mp: 122-123 °C Lit (122-124 °C).⁸⁵

8-(3-Chloroprop-1-ynyl)-2,8-dimethoxybicyclo[4.2.0]octa-1,3,5-triene 3.18



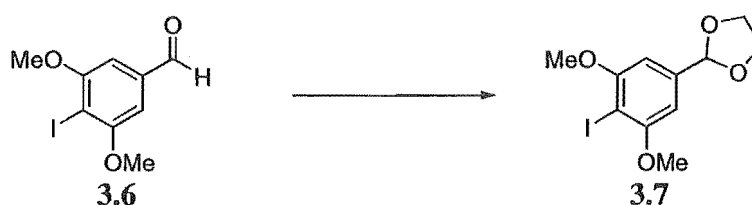
Freshly prepared Ag₂O was added to a solution of the alcohol **2.61** in iodomethane (3 mL). The reaction was protected from light and stirred in a stoppered flask overnight. The resulting solution was evaporated to dryness and the residue purified by flash chromatography on silica gel, eluting with 10 % EtOAc/petroleum ether, to give the title compound as a colourless oil (0.148 g, 93 %).

^1H NMR (300 MHz, CDCl_3): δ 3.47 [m, 2H], 3.51 [s, 3H], 3.98 [s, 3H], 4.20 [s, 2H], 6.75 [m, 2H], 7.26 [dd, $J = 8.3, 7.3$ Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 30.3, 44.5, 53.7, 56.8, 75.5, 80.3, 85.5, 113.4, 115.8, 129.22, 131.8, 143.2, 153.3.

HRMS: Calcd for $\text{C}_{13}\text{H}_{13}\text{ClO}_2$ (M^+) 236.0604, found 236.0604.

2-(4-Iodo-3,5-dimethoxyphenyl)-1,3-dioxolane 3.7



A solution of the aldehyde **3.6** (3.42 g, 11.7 mmol), 1,2-ethanediol (0.98 mL, 17.6 mmol), and *p*-toluenesulfonic acid (40 mg, 0.21 mmol) in benzene (80 mL) was heated at reflux under Dean-Stark conditions for 20 h. After this time Et_2O (100 mL) and sat aq NaHCO_3 solution were added. The organic extract was washed with water and the solvent removed under reduced pressure to give the title compound as a white solid (3.89 g, 99%).

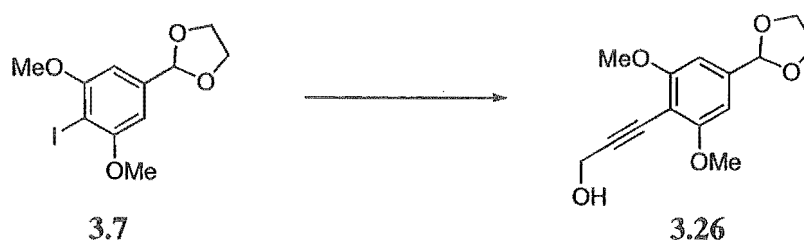
Mp: 82-83 $^\circ\text{C}$.

^1H NMR (300 MHz, CDCl_3): δ 3.91 [s, 3H], 4.00-4.17 [m, 4H], 5.80 [s, 1H], 6.64 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 56.6, 65.3, 78.2, 102.0, 103.1, 140.3, 159.4.

HRMS: Calcd for $\text{C}_{11}\text{H}_{13}\text{IO}_4$ (M^+) 335.9857, found 335.9859.

3-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-prop-2-yn-1-ol 3.26



A solution of the iodide **3.7** (1.23 g, 3.67 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.193 g, 0.275 mmol) in pyrrolidine (12 mL) was stirred at r.t. for 5 min. Propargyl alcohol (0.427 mL, 7.34 mmol) was added followed by stirring for 5 min, then addition of CuI (70 mg, 0.376 mmol). The reaction heated at reflux for 75 min. The resulting solution was poured into sat aq NH_4Cl solution (800 mL) and extracted with EtOAc (x4). The combined organic extracts were washed in turn with 10 % w/v aq $\text{Na}_2\text{S}_2\text{O}_3$ solution and water. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 75 % EtOAc/petroleum ether, gave the title compound as a white solid (0.764 g, 79 %).

Mp: 106-107 °C.

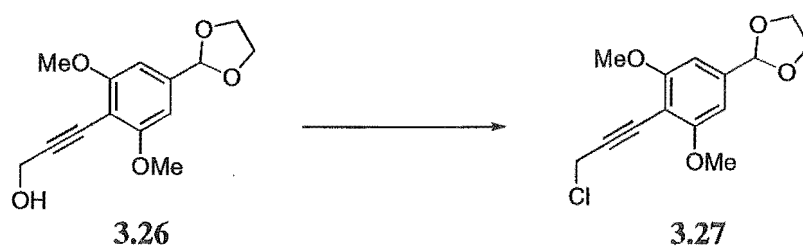
^1H NMR (300 MHz, CDCl_3): δ 3.88 [s, 6H], 4.00 – 4.16 [m, 4H], 4.57 [s, 2H], 5.77 [s, 1H], 6.66 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 51.5, 55.8, 65.0, 77.2, 96.3, 101.1, 101.2, 102.9, 139.7, 161.1.

IR (film): 2240, 3419 cm^{-1} .

HRMS: Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_5$ (M^+) 264.0998, found 264.0998

2-[4-(3-Chloroprop-1-ynyl)-3,5-dimethoxyphenyl]-1,3-dioxolane **3.27**



DMAP (0.179 g, 1.46 mmol), NEt_3 (340 mL), and TsCl were added to a solution of the alcohol **3.26** (0.644 g, 2.44 mmol) in dry CH_2Cl_2 . The resulting solution was stirred at r.t. for 1h, then diluted with Et_2O and H_2O . The aqueous layer was extracted with a further two portions of Et_2O and the combined organic extracts washed with satd NaHCO_3 solution. Removal of the solvent under reduced pressure gave the title compound as a white solid (0.412 g, 60 %).

Mp: 157-158 °C.

^1H NMR (300 MHz, CDCl_3): δ 3.89 [s, 6H], 4.02-4.15 [m, 4H], 4.49 [s, 2H], 5.78 [s, 1H], 6.66 [s, 2H].

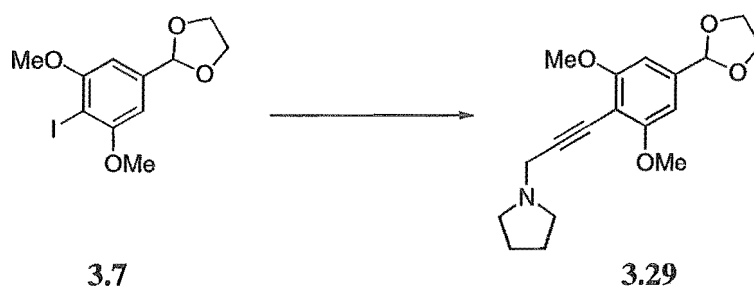
^{13}C NMR (75 MHz, CDCl_3): δ 31.7, 56.0, 65.1, 78.7, 92.2, 100.7, 101.3, 103.0, 140.5, 161.6.

IR (film): 2255 cm^{-1} .

HRMS: electrospray Calcd for $\text{C}_{14}\text{H}_{15}\text{ClO}_4$ (M^+) 282.0659, found 282.0659.

1-{3-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-prop-2-ynyl}-pyrrolidine

3.29



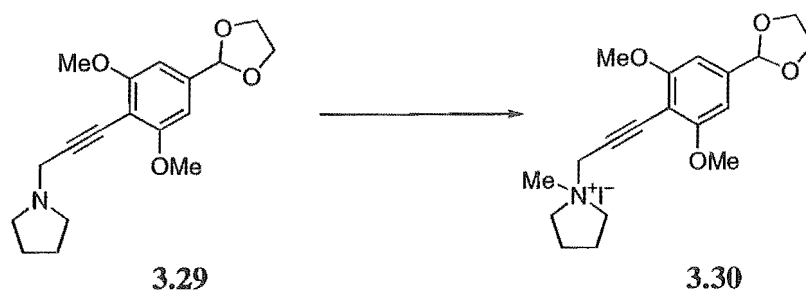
A solution of the iodide **3.7** (0.206 g, 0.614 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (32 mg, 0.460 mmol) in pyrrolidine (2 mL) was stirred at r.t. for 5 min. Propargyl chloride (43 wt %, 0.231 mL, 12.3 mmol) in benzene was added, followed by stirring for 5 min, then addition of CuI (12 mg). The reaction heated at reflux for 75 min. The resulting solution was poured into H_2O and extracted with EtOAc (x4). The combined organic extracts were washed with 10 % w/v aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 5 % MeOH/ CH_2Cl_2 , gave the title compound as a tan solid (0.155 g, 80 %).

Mp: 75-78 $^\circ\text{C}$.

^1H NMR (300 MHz, CDCl_3): δ 1.83 [m, 4H], 2.75 [m, 4H], 3.76 [s, 2H], 3.87 [s, 6H], 3.99-4.16 [m, 4H], 5.77 [s, 1H], 6.65 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 23.8, 44.0, 52.0, 55.9, 65.1, 76.5, 94.2, 101.3, 102.0, 103.1, 139.1, 161.2.

HRMS: Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4$ (M^+) 317.1627, found 317.1627.

1-{3-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-prop-2-ynyl}-1-methylpyrrolidinium; iodide 3.30

Iodomethane (31 μ L, 0.498 mmol) was added to a solution of the amine **3.29** (79 mg, 0.249 mmol) in dry acetone (0.65 mL) and the reaction was stirred for 90 min at r.t. The solvent was removed under reduced pressure to give a solid that was washed with ether and dried under reduced pressure to give the title compound as a white solid (0.106 g, 93 %).

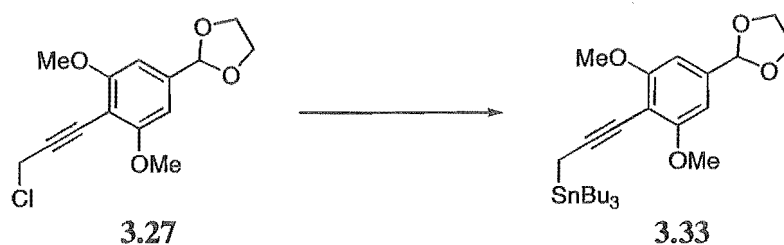
Mp: 208-209 $^{\circ}$ C.

1 H NMR (500 MHz, CDCl_3): δ 2.24-2.45 [m, 4H], 3.58 [s, 3H], 3.87 [s, 6H], 3.92-4.16 [overlapping m's, 8H], 4.76 [s, 2H], 5.76 [s, 1H], 6.65 [s, 2H].

13 C NMR (75 MHz, CDCl_3): δ 21.8, 49.8, 54.8, 55.8, 63.5, 64.9, 84.0, 84.6, 98.8, 101.0, 102.5, 141.2, 161.3.

IR (film): 2235, 3320 cm^{-1} .

HRMS: electrospray Calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_4$ (M^+) 332.1862, found 332.1861.

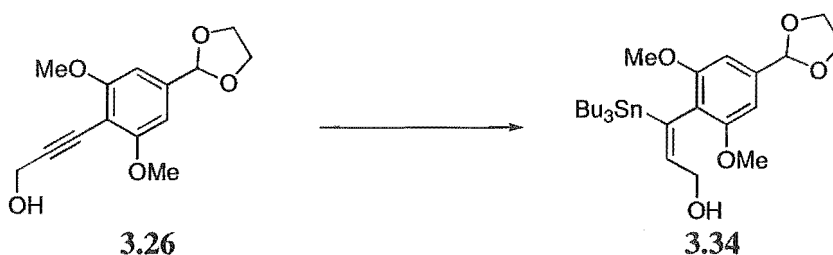
Tributyl-{3-[4-(1,3)-dioxolan-2-yl-2,6-dimethoxyphenyl]-prop-2-ynyl}-stannane 3.33

A solution of the chloride **3.27**, $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{PPh}_3)_4$ (10 mol %), and hexabutylditin in dry THF (2 ml) was heated at reflux for 24h. The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 25 % EtOAc/petroleum ether, to give the title compound as a colourless oil (13-40 %). Unfortunately, this compound decomposed before characterisation could be completed.

^1H NMR (500 MHz, CDCl_3): δ 0.87 [m, 9H], 1.04 [m, 6H], 1.33 [m, 6H], 1.55 [m, 6H], 1.90 [t, $J_{\text{Sn-H}} = 25$ Hz, 2H], 3.86 [s, 6H], 4.00 - 4.15 [m, 4H], 5.77 [s, 1H], 6.63 [s, 2H].

HRMS: Calcd for $\text{C}_{26}\text{H}_{42}\text{SnO}_4$ ($\text{M}^+ - \text{Bu}$) 481.1401, found 481.1401.

(E)-3-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-3-tributylstannanylprop-2-en-1-ol 3.34



HSnBu_3 (1.10 mL, 4.07 mmol) was added to a solution of the acetylene **3.26** (0.673 g, 2.55 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (18 mg, 0.0255 mmol) in dry THF (3.5 mL). The reaction was stirred for 10 min at r.t. and the solvent removed under reduced pressure. The resulting brown oil was purified by flash chromatography, eluting with 40 % EtOAc/petroleum ether, to give the title compound as a colourless oil (1.28 g, 90 %).

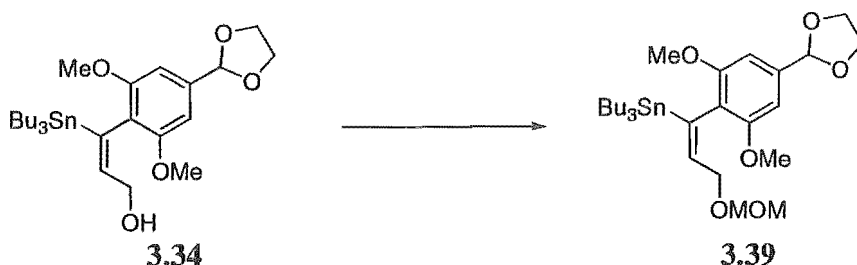
^1H NMR (300 MHz, CDCl_3): δ 0.83 [m, 15H], 1.22 [m, 6H], 1.40 [m, 6H], 1.96 [br s, 1H] 3.76 [s, 6H], 3.81 [d, $J = 6.8$ Hz, 2H], 3.98 - 4.19 [m, 4H], 5.77 [s, 1H], 6.14 [tt, $J = 32, 6.8$ Hz, 1H], 6.67 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 10.1, 13.6, 27.1, 28.7, 55.4, 61.1, 65.0, 101.7, 103.5, 121.0, 136.4, 140.3, 140.5, 155.0.

IR (film): 1578, 3490 cm^{-1} .

HRMS: Calcd for $\text{C}_{26}\text{H}_{44}\text{SnO}_5$ ($\text{M}^+ - \text{Bu}$) 499.1507, found 499.1507.

(E)-Tributyl-{1-[4-(1,3)-dioxolan-2-yl-2,6-dimethoxyphenyl]-3-methoxymethoxypropenyl}-stannane 3.39



i Pr₂NEt (86 μ L, 0.49 mmol) was added to solution of the alcohol **3.34** (0.109 g, 0.196 mmol) in dry CH₂Cl₂ at 0 °C. Following this, MOM-Cl (30 μ L, 0.392 mmol) was slowly added and the reaction was allowed to warm slowly to r.t. and stirred for 48 h. Sat aq NaHCO₃ solution was added and the product extracted with EtOAc (x 4). The combined organic extracts were washed with H₂O. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 30 % EtOAc/petroleum ether, gave the title compound as a colourless oil which solidified on standing to give a white solid (0.118 g, 100 %).

Mp: 54-55 °C.

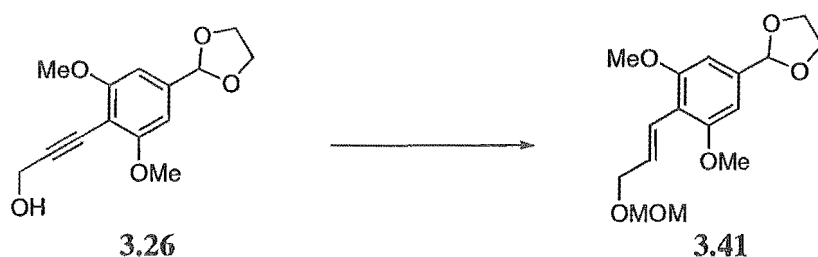
¹H NMR (300 MHz, CDCl₃): δ 0.83 [m, 15H], 1.25 [m, 6H], 1.40 [m, 6H], 3.28 [s, 3H], 3.74 [s, 6H], 3.88 [m, 2H], 3.98 – 4.20 [m, 4H], 4.55 [s, 2H], 5.77 [s, 1H], 5.93 [m, 1H], 6.63 [s, 2H].

¹³C NMR (75 MHz, CDCl₃): δ 10.3, 13.7, 27.3, 28.8, 55.0, 55.4, 65.2, 66.6, 95.8, 101.4, 103.9, 121.2, 136.3, 138.3, 139.3, 155.3.

IR (KBr): 1618, 1622 cm⁻¹.

HRMS: Calcd for C₂₈H₄₈SnO₆ (M⁺ - Bu) 543.1769, found 543.1769.

(E)-2-[3,5-Dimethoxy-4-(3-methoxymethoxypropenyl)]-1,3-dioxolane 3.41



A solution of the acetylene **3.26** (30.5 mg, 0.115 mmol) in dry THF (1.2 mL) was added to a suspension of LiAlH_4 (22 mg, 0.577 mmol) in dry THF (0.6 mL) at 0 °C. The reaction was warmed to r.t. and stirred overnight. The resulting solution was cooled to 0 °C and quenched by slow addition of H_2O . The product was extracted with EtOAc (x 4) and the combined organic extracts were washed with H_2O . Removal of the solvent under reduced pressure gave a residue (44mg) which was dissolved in dry CH_2Cl_2 (1.2 mL). The resulting solution was cooled to 0 °C and $i\text{-Pr}_2\text{NEt}$ (50 μL , 0.288 mmol) was added followed by MOM-Cl (18 μL , 0.231 mmol). The reaction was allowed to warm to r.t. overnight and quenched by addition of sat aq NaHCO_3 solution. The product was extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 40 % EtOAc/petroleum ether, gave the title compound as a colourless oil (23 mg, 65 %).

^1H NMR (300 MHz, CDCl_3): δ 3.40 [s, 3H], 3.85 [s, 6H], 3.97-4.16 [m, 4H], 4.23 [dd, $J = 6.4$, 0.98 Hz, 1H], 4.70 [s, 2H], 5.76 [s, 1H], 6.67 [s, 2H], 6.71 [dt, $J = 16$, 6.4 Hz, 1H], 6.89 [d, $J = 16$ Hz, 1H]

^{13}C NMR (75 MHz, CDCl_3): δ 55.2, 55.7, 65.2, 69.6, 95.5, 101.7, 103.4, 114.4, 123.0, 129.8, 137.9, 158.4.

IR (film): 1609 cm^{-1} .

HRMS: Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$ (M^+) 310.1416, found 310.1416.

(*E*)-3-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-3-iodoprop-2-en-1-ol **3.43**



I_2 (0.222 g, 1.75 mmol) was added to a solution of the stannane **3.34** (0.486 g, 0.876 mmol) in dry CH_2Cl_2 (9 mL). The reaction was stirred for 5 min at r.t. then quenched by addition of sat aq NaHCO_3 solution. The product was extracted with EtOAc (x 4) and the combined organic extracts were washed with 10 % w/v aq $\text{Na}_2\text{S}_2\text{O}_3$ solution. Removal of the solvent under

reduced pressure and purification by flash chromatography, eluting with 70 % EtOAc/petroleum ether, gave the title compound as a colourless gum which solidified on standing to give a white solid (0.289 g, 84 %).

Mp: 87-88 °C.

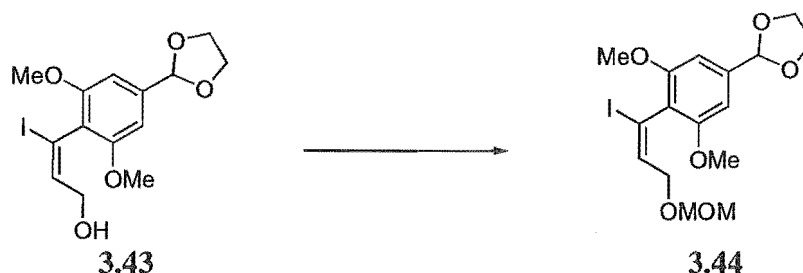
¹H NMR (300 MHz, CDCl₃): δ 3.69 [d, *J* = 7.3 Hz, 2H], 3.88 [s, 6H], 4.00 - 4.18 [m, 4H], 5.76 [s, 1H], 6.88 [s, 2H], 6.81 [t, *J* = 7.3 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 56.0, 61.5, 65.1, 89.3, 102.1, 103.0, 118.3, 140.1, 143.4, 156.4.

IR (KBr): 1640, 3425 cm⁻¹.

HRMS: electrospray Calcd for C₁₄H₁₈IO₅ (M⁺) 393.0199, found 393.0218.

(*E*)-2-[4-(Iodo-3-methoxymethoxypropenyl)-3,5-dimethoxyphenyl]-1,3-dioxolane 3.44



*i*Pr₂NEt (279 mL, 1.60 mmol) was added to a solution of the alcohol **3.43** (0.251 g, 0.640 mmol) in dry CH₂Cl₂ (6 mL) at 0 °C. Following this MOM-Cl (97 mL, 1.28 mmol) was slowly added. The reaction was allowed to warm slowly to r.t. and stirred for 40 h then quenched by addition of sat aq NaHCO₃ solution. The product was extracted with EtOAc (x 4) and the combined organic extracts washed with H₂O. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60 % EtOAc/petroleum ether, gave the title compound as a pale yellow oil (0.281 g, 100 %).

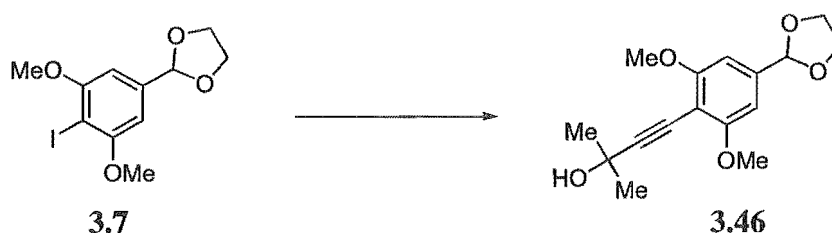
¹H NMR (300 MHz, CDCl₃): δ 3.24 [s, 3H], 3.71 [d, *J* = 6.4 Hz, 2H], 3.85 [s, 6H], 3.99-4.18 [m, 4H], 4.50 [s, 2H], 5.76 [s, 1H], 6.64 [s, 2H], 6.67 [t, *J* = 6.1 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 54.6, 55.5, 64.8, 65.4, 88.4, 95.0, 101.4, 102.8, 117.9, 139.9, 141.0, 156.1.

IR (film): 1605 cm^{-1} .

HRMS: electrospray Calcd for $\text{C}_{16}\text{H}_{21}\text{IO}_6$ ($\text{M}^+ + \text{Na}$) 459.0281, found 459.0283.

4-[4-(1,3)-Dioxolan-2-yl-2,6-dimethoxyphenyl]-2-methylbut-3-yn-2-ol 3.46



A solution of the iodide **3.7** (0.536 g, 1.60 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (84 mg, 0.120 mmol) in pyrrolidine (5 mL) was stirred at r.t. for 5 min. 2-Methyl-3-butyn-2-ol (0.310 mL, 3.20 mmol) was added followed by stirring for a further 5 min, then addition of CuI (30 mg, 0.160 mmol). The reaction was heated at reflux for 75 min and the resulting solution was poured into sat aq NH_4Cl solution (350 mL) and extracted with EtOAc (x4). The combined organic extracts were washed in turn with 10 % w/v aq $\text{Na}_2\text{S}_2\text{O}_3$ solution and water. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60 % EtOAc/petroleum ether, gave the title compound as a pale yellow solid (0.406 g, 87 %).

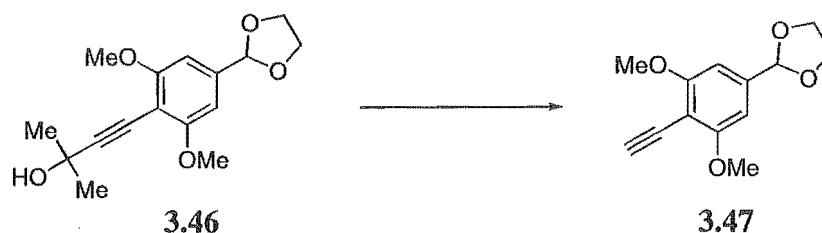
Mp: 114-115 $^\circ\text{C}$.

^1H NMR (300 MHz, CDCl_3): δ 1.63 [s, 6H], 3.86 [s, 6H], 3.98-4.15 [m, 4H], 5.76 [s, 1H], 6.63 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 31.3, 55.8, 65.0, 65.3, 73.9, 101.3, 101.4, 102.9, 103.0, 139.3, 160.9.

IR (KBr): 3418 cm^{-1} .

HRMS: Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_5$ (M^+) 292.1311, found 292.1311.

2-(4-Ethynyl-3,5-dimethoxyphenyl)-1,3-dioxolane 3.47

A solution of the alcohol **3.46** (0.390 g, 1.33 mmol) and NaOH (100 mg) in dry toluene (10 mL) was heated at reflux for 3 h. The reaction was quenched by addition of sat aq NH_4Cl solution and extracted with ether (x 4). Removal of the solvent under reduced pressure gave a residue which was purified by flash chromatography, eluting with 40 % EtOAc/petroleum ether, to give the title compound as a tan solid (0.297 g, 95 %).

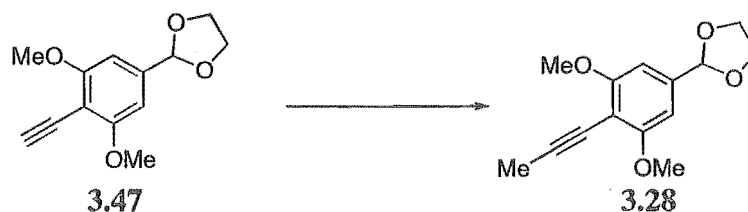
Mp: 82-83 °C.

^1H NMR (300 MHz, CDCl_3): δ 3.57 [s, 1H], 3.91 [s, 6H], 3.99-4.15 [m, 4H], 5.78 [s, 1H], 6.67 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 55.9, 65.0, 75.9, 85.5, 100.3, 101.1, 102.8, 140.3, 161.7.

IR (KBr): 2200, 3273 cm^{-1} .

HRMS: Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4$ (M^+) 234.0892, found 234.0892.

2-(3,5-Dimethoxy-4-prop-1-ynylphenyl)-1,3-dioxolane 3.28

A solution of *n*-BuLi (1.57 M, 1.74 mL, 2.74 mmol) in hexane was added dropwise to a solution of the alkyne **3.47** (0.291 g, 1.24 mmol) in dry THF (6 mL) at 0 °C. The reaction was stirred for 20 min at 0 °C then CH_3I (0.465 mL, 7.46 mmol) was added and the reaction warmed slowly to r.t. overnight. Sat aq NH_4Cl solution was added and the product extracted with EtOAc (x 4).

The combined organic extracts were washed with 10 % w/v aq $\text{Na}_2\text{S}_2\text{O}_4$ solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 40 % EtOAc/petroleum ether, gave the title compound as a white solid (0.156 g, 51 %).

Mp: 122-123 °C.

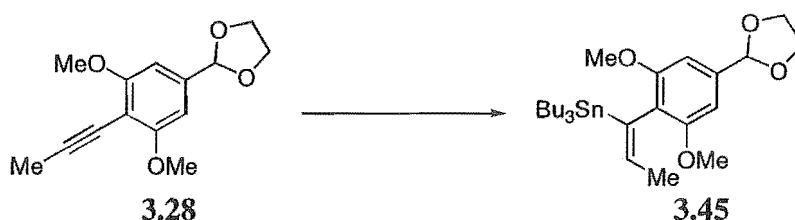
^1H NMR (300 MHz, CDCl_3): δ 2.18 [s, 3H], 3.89 [s, 6H], 3.99-4.17 [m, 4H], 5.77 [s, 1H], 6.66 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 4.97, 55.8, 65.0, 71.3, 94.7, 101.2, 102.2, 103.0, 138.6, 161.0.

IR (KBr): 2250 cm^{-1} .

HRMS: Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4$ (M^+) 248.1049, found 248.1049.

(*E*)-Tributyl-{1-[4-(1,3)-dioxolan-2-yl-2,6-dimethoxyphenyl]-propenyl}-stannane 3.45



HSnBu_3 (250 μL , 0.925 mmol) was slowly added to a solution of the acetylene **3.28** (0.144 g, 0.578 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (4 mg, 0.0058 mmol) in dry THF (0.75 mL). The reaction was stirred for 10 min at r.t. and the solvent removed under reduced pressure. The resulting brown oil was purified by flash chromatography, eluting with 15 % EtOAc/petroleum ether, to give the title compound as a colourless oil (0.270 g, 87 %).

^1H NMR (300 MHz, CDCl_3): δ 0.81 [m, 15H], 1.20-1.45 [m, 12H], 1.51 [d, $J = 5.9$ Hz, 3H], 3.76 [s, 6H], 3.99-4.22 [m, 4H], 5.78 [s, 1H], 5.93 [tq, $J = 33, 6.4$ Hz, 1H], 6.66 [s, 2H].

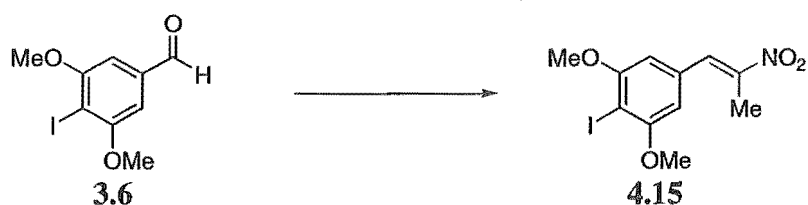
^{13}C NMR (75 MHz, CDCl_3): δ 10.1, 13.7, 16.8, 27.3, 28.9, 55.4, 65.1, 101.4, 103.9, 121.9, 135.7, 137.1, 137.2, 155.6.

IR (film): 1578 cm^{-1} .

HRMS: Calcd for $\text{C}_{26}\text{H}_{44}\text{SnO}_4$ ($\text{M}^+ - \text{Bu}$) 483.1558, found 483.1558.

6.5 Experiments Described in Chapter 4

(*E*)-2-Iodo-1,3-dimethoxy-5-(2-nitropropenyl)-benzene 4.15



A solution of the aldehyde **3.6** (1.71 g, 5.86 mmol), ammonium acetate (244 mg), and glacial acetic acid (2 mL) in nitroethane (5 mL) was heated at reflux for 4h. The resulting solution was poured into sat aq NaHCO₃ solution and extracted with EtOAc (x 4). Removal of the solvent under reduced pressure gave a residue that was recrystallised from MeOH to give the title compound as yellow needles (0.973 g). Concentration of the mother liquor yielded a further 0.332 g of crystals. Flash chromatography of the remaining residue gave an extra 0.132 g giving a total of 1.44 g, (70 %).

Mp: 130-131 °C.

¹H NMR (500 MHz, CDCl₃): δ 2.46 [d, *J* = 0.98 Hz, 3H], 3.92 [s, 6H], 6.51 [s, 2H], 8.04 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 14.1, 56.6, 80.1, 105.2, 133.0, 134.0, 148.1, 159.5.

IR (KBr): 1510, 1568 cm⁻¹.

HRMS: Electrospray Calcd for C₁₁H₁₂INO₄ (M⁺) 348.9810, found 348.9811.

1-(4-Iodo-3,5-dimethoxyphenyl)-propan-2-one 4.16



A solution of the nitrostyrene **4.15** (1.30 g, 3.72 mmol) and Fe powder (2.56 g) in glacial acetic acid (35 mL) was heated at reflux for 3 h. The resulting solution was diluted with H₂O (300 mL) and extracted with Et₂O (x 4). The combined organic extracts were washed with 1 M NaOH

solution and the solvent removed under reduced pressure to give the title compound as a white solid (1.12 g, 94 %).

Mp: 88-89 °C.

^1H NMR (500 MHz, CDCl_3): δ 2.17 [s, 3H], 3.67 [s, 2H], 3.87 [s, 6H], 6.34 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 29.2, 50.9, 56.4, 75.8, 105.2, 136.3, 159.3, 205.5.

IR (KBr): 1717 cm^{-1} .

HRMS: Electrospray Calcd for $\text{C}_{11}\text{H}_{13}\text{IO}_3$ (M^+) 319.9908, found 319.9910.

(±)-1-(4-Iodo-2,5-dimethoxyphenyl)-propan-2-ol rac-4.17



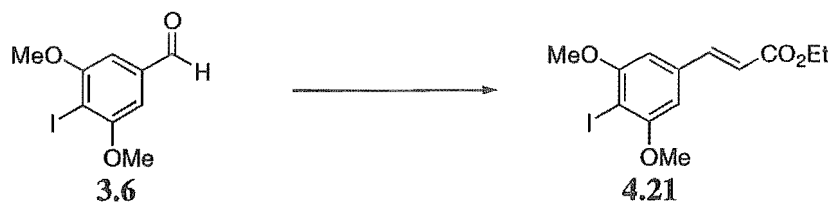
A solution of DIBAL (1.0 M, 3.85 mL, 3.85 mmol) in dry CH_2Cl_2 was added dropwise to a solution of the ketone **4.16** (1.12 g, 3.50 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. The reaction was warmed to r.t. and stirred for 30 min, then recooled to 0 °C and quenched by slow addition of H_2O until coagulation occurred. The suspension was diluted with 1 M HCl solution then extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, eluting with 50 % EtOAc/petroleum ether, gave the title compound as a colourless, viscous oil (1.07 g, 95 %).

^1H NMR (500 MHz, CDCl_3): δ 1.25 [d, J = 6.4 Hz, 3H], 2.65 [dd, J = 13, 8.3 Hz, 1H], 2.76 [dd, J = 14, 4.4 Hz, 1H], 3.87 [s, 6H], 4.01 [m, 1H], 6.36 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 22.7, 45.8, 56.3, 68.4, 74.1, 105.1, 140.9, 159.0.

IR (film): 3385, 3547 cm^{-1} .

HRMS: Electrospray Calcd for $\text{C}_{11}\text{H}_{15}\text{IO}_3$ (M^+) 322.0066, found 322.0065.

(*E*)-3-(4-Iodo-3,5-dimethoxyphenyl)-acrylic acid ethyl ester 4.21

Triethyl phosphonoacetate (1.58 mL, 7.94 mmol) was added to a suspension of prewashed NaH (208 mg, 8.67 mmol) in dry benzene (20 mL) at 0 °C. The reaction was stirred for 15 min then a solution of the aldehyde 3.6 (2.11 g, 7.22 mmol) in dry benzene (30 mL) was slowly added. The reaction was stirred for 1 h at 0 °C, then 30 min at r.t., following which H₂O was added. The aqueous layer was extracted with EtOAc (x 4) and the combined organic extracts were washed with H₂O (x 2). Removal of the solvent under reduced pressure gave the title compound as a white solid (2.62 g, 100 %).

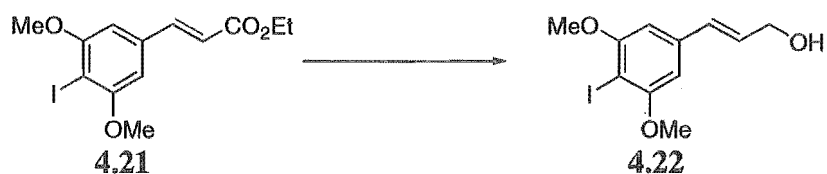
Mp: 135-136 °C.

¹H NMR (500 MHz, CDCl₃): δ 1.34 [t, *J* = 7.3 Hz, 3H], 3.92 [s, 6H], 4.27 [q, *J* = 7.3 Hz, 2H], 6.47 [d, *J* = 16 Hz, 1H], 6.63 [s, 2H], 7.62 [d, *J* = 16 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 14.2, 56.4, 60.5, 80.2, 103.2, 118.9, 136.1, 143.7, 159.5, 166.5.

IR (KBr): 1703 cm⁻¹.

HRMS: Calcd for C₁₃H₁₅IO₄ (M⁺) 362.0014, found 362.0015.

(*E*)-3-(4-Iodo-3,5-dimethoxyphenyl)-prop-2-en-1-ol 4.22

Neat DIBAL (2.88 mL, 16.2 mmol) was added dropwise to a solution of the ester 4.21 (2.34 g, 6.47 mmol) in dry CH₂Cl₂ (40 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched by dropwise addition of H₂O until coagulation occurred. The suspension was diluted with 1 M HCl solution and extracted with EtOAc (x 4). Removal of the solvent under reduced

pressure and purification of the residue by flash chromatography, eluting with 70 % EtOAc/petroleum ether, gave the title compound as a white solid (1.65 g, 80 %).

Mp: 122-123 °C.

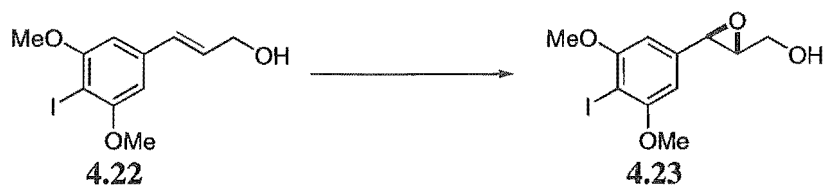
¹H NMR (500 MHz, CDCl₃): δ 3.89 [s, 6H], 4.34 [d, *J* = 4.9 Hz, 2H], 6.41 [dt, *J* = 16, 5.4 Hz, 1H], 6.53 [s, 2H], 6.58 [dd, *J* = 16, 1.5 Hz, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 56.4, 63.1, 76.5, 102.1, 129.5, 130.1, 138.6, 159.2.

IR (film): 3209 cm⁻¹.

HRMS: Calcd for C₁₁H₁₃IO₃ (M⁺) 319.9908, found 319.9910.

[3-(4-Iodo-3,5-dimethoxyphenyl)-(2*S*,3*R*)-oxiranyl]-methanol 4.23



Ti(OiPr)₄ (50 μL, 0.168 mmol) was added to a solution of diisopropyl-*D*-tartrate (47 mg, 0.202 mmol) and powdered 4Å molecular sieves (100 mg) in dry CH₂Cl₂ (12 mL) at -20 °C. Anhydrous TBHP solution in CH₂Cl₂ (6.1 M, 1.10 mL, 6.72 mmol) was added at such a rate as to maintain the internal temp at -20 °C. The reaction was stirred for 30 min at this temperature following which a solution of the allylic alcohol 4.22 (1.07 g, 3.35 mmol) in dry CH₂Cl₂ (11 mL), previously stirred over 4Å sieves for 30 min, was added at a rate as to maintain the internal temperature between -15 and -20 °C. The reaction was stirred for 5 h at -20 °C then 10 % aq NaOH solution, saturated with brine (6 mL), was added, followed by ether (40 mL). The solution was warmed to r.t. then dry MgSO₄ (6.5 g) and celite (0.83 g) were added. The suspension was stirred for 15 min, diluted with CH₂Cl₂, and filtered through a pad of celite, rinsing with CH₂Cl₂. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 70 % EtOAc/petroleum ether, gave the title compound as a white solid (0.947 g, 84 %, 90 % ee). Recrystallisation from benzene/petroleum ether gave (0.821 g, 73 %, > 95 % ee).

$[\alpha]_D^{20} + 23.5$ (c 5.61, CHCl_3)

Mp: 99-100 °C.

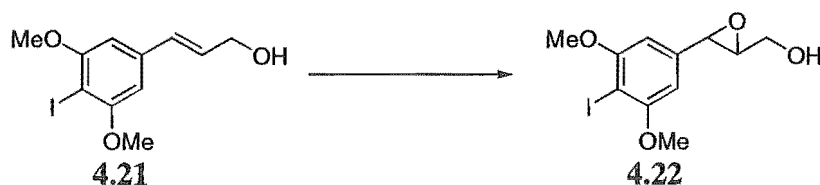
^1H NMR (500 MHz, CDCl_3): δ 1.82 [d, $J = 7.8$ Hz, 1H], 3.17 [m, 1H], 3.82 [m, 1H], 3.88 [s, 6H], 3.94 [d, $J = 2.0$ Hz, 1H], 4.06 [m, 1H], 6.44 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 55.3, 56.5, 60.9, 62.6, 76.8, 101.1, 139.3, 159.5.

IR (KBr): 3412 cm^{-1} .

HRMS: Calcd for $\text{C}_{11}\text{H}_{13}\text{IO}_4$ (M^+) 335.9857, found 335.9859.

[3-(4-Iodo-3,5-dimethoxyphenyl)-2,3-oxiranyl]-methanol rac-4.23



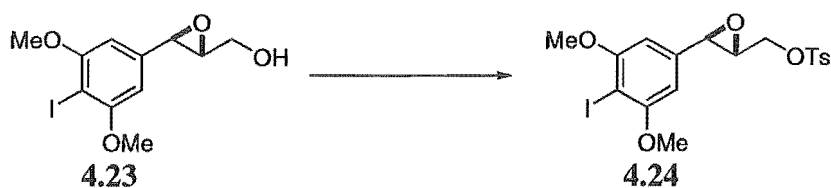
Anhydrous TBHP solution (6.1 M, 6.72 mmol) in CH_2Cl_2 (52 μL) was added to a solution of the allylic alcohol (50 mg, 0.16 mmol) **4.22** and $\text{VO}(\text{acac})_2$ (0.8 mg, 0.31 μmol) in dry CH_2Cl_2 (0.5 mL). The reaction was stirred for 1 h at r.t., diluted with CH_2Cl_2 , and filtered through a plug of celite. The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 70 % EtOAc/petroleum ether, to give the title compound as a white solid (48 mg, 91 %), which was identical to the chiral material prepared above.

Preparation and analysis of the Mosher esters derived from epoxide 4.23

Dry NEt_3 (10 μL), and a solution of (*S*)-MTPA-Cl (33 mg/mL) in dry CH_2Cl_2 (140 μL), were added to a solution of the epoxide **4.23** (5 mg) and DMAP (2 mg) in dry CH_2Cl_2 (0.5 mL). The reaction was stirred for 10 min at r.t., followed by TLC analysis to ensure complete consumption of starting material. The resulting solution was filtered through a short silica gel column, eluting with 40 % EtOAc/petroleum ether, and the solvent removed under reduced pressure. The enantiomeric excess for the epoxidation was determined by integration of the multiplets in the ^1H NMR spectrum ($d_1=5$) at 3.21 and 3.25 ppm.

Major diastereoisomer: ^1H NMR (500 MHz, CDCl_3): δ 3.25 [m, 1H], 3.58 [s, 3H], 3.80 [d, $J = 2.0$ Hz, 1H], 3.87 [s, 3H], 4.40 [dd, $J = 12, 4.4$ Hz, 1H], 4.72 [dd, $J = 12, 3.4$ Hz, 1H], 6.37 [s, 2H], 7.41 [m, 3H], 7.54 [m, 2H].

Toluene-4-sulfonic acid 3-(4-iodo-3,5-dimethoxyphenyl)-(2*S*,3*R*)-oxiranyl methyl ester 4.24



Dry NEt_3 (1.69 mL, 12.2 mmol) was added to a solution of the alcohol **4.23** (0.816 g, 2.43 mmol) and DMAP (0.297 g, 2.43 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. A solution of TsCl (0.510 g, 2.67 mmol) in dry CH_2Cl_2 (3 mL) was slowly added. The reaction was stirred at 0 °C for 1 h, diluted with CH_2Cl_2 , and washed in turn with 1 M HCl solution and sat aq NaHCO_3 solution. Removal of the solvent under reduced pressure gave the title compound as a fluffy white solid (1.13 g, 95 %).

$[\alpha]_{\text{D}}^{20} + 32.6$ (c 2.61, CHCl_3)

Mp: 48–49 °C.

^1H NMR (500 MHz, CDCl_3): δ 2.45 [s, 3H], 3.19 [m, 1H], 3.80 [d, $J = 2.0$ Hz, 1H], 3.86 [s, 6H], 4.15 [dd, $J = 12, 4.2$ Hz, 1H], 4.33 [dd, $J = 12, 3.4$ Hz, 1H], 6.37 [s, 2H], 7.35 [d, $J = 8.3$ Hz, 2H], 7.81 [d, $J = 8.3$ Hz, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 21.5, 56.0, 56.4, 58.5, 69.0, 77.2, 101.0, 127.8, 129.8, 132.3, 138.1, 145.1, 159.4.

HRMS: Calcd for $\text{C}_{18}\text{H}_{19}\text{IO}_6\text{S}$ (M^+) 489.9946, found 489.9947.

(2R)-1-(4-Iodo-3,5-dimethoxyphenyl)-propan-2-ol 4.17

Neat DIBAL (1.23 mL, 6.91 mmol) was added dropwise to a solution of the tosylate **4.24** (1.13 g, 2.30 mmol) in dry CH_2Cl_2 (35 mL) at -15°C . The resulting solution was stirred for 2 h at -15°C , then allowed to warm to r.t. overnight. The reaction was quenched by dropwise addition of H_2O , till coagulation occurred. The suspension was diluted with 1 M HCl solution then extracted with EtOAc (x 4). The combined organic extracts were washed with sat aq NaHCO_3 solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 60 % EtOAc/petroleum ether, gave the title compound as a colourless viscous oil (0.693 g, 94 %).

$[\alpha]_{\text{D}}^{20} -16.4$ (c 6.35, CHCl_3)

^1H NMR (500 MHz, CDCl_3): δ 1.25 [d, $J = 6.4$ Hz, 3H], 2.65 [dd, $J = 13, 8.3$ Hz, 1H], 2.76 [dd, $J = 14, 4.4$ Hz, 1H], 3.87 [s, 3H], 4.01 [m, 1H], 6.36 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 22.7, 45.8, 56.3, 68.4, 74.1, 105.1, 140.9, 159.0.

IR (film): 3385, 3547 cm^{-1} .

HRMS: Calcd for $\text{C}_{11}\text{H}_{15}\text{IO}_3$ (M^+) 322.0066, found 322.0065.

(1S)-2-[2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethyl]-isoindole-1,3-dione 4.18

DEAD (0.422 mL, 0.570 mmol) was added to a solution of the alcohol **4.17** (0.693 g, 2.15 mmol), PPh_3 (0.705 g, 2.69 mmol), and phthalimide (0.396 g, 2.69 mmol) in dry THF (20 mL) at 0 °C. The reaction was protected from light and allowed to warm to r.t. overnight. Sat aq NaHCO_3 solution was added and the product extracted with EtOAc (x 4). The combined organic extracts were washed with sat aq NaHCO_3 solution. The solvent was removed under reduced pressure and purification by flash chromatography, eluting with 25 % EtOAc/petroleum ether, gave the title compound as a white solid (0.786 g, 81 %).

$[\alpha]_D^{20} + 120$ (c 2.92, CHCl_3)

Mp: 124-125 °C.

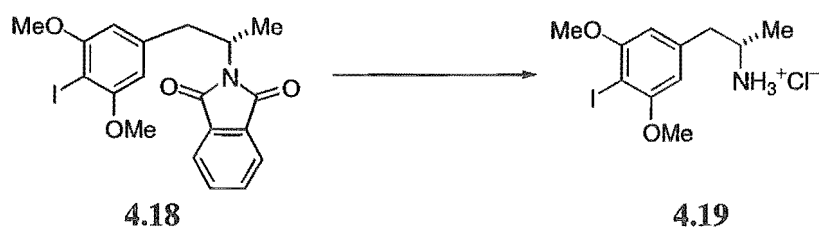
^1H NMR (500 MHz, CDCl_3): δ 1.55 [d, $J = 6.8$ Hz, 3H], 3.06 [dd, $J = 14, 6.4$ Hz, 1H], 3.37 [dd, $J = 10, 14$ Hz, 1H], 3.76 [s, 6H], 4.70 [m, 1H], 6.32 [s, 2H], 7.67 [m, 2H], 7.75 [m, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 18.4, 39.8, 47.8, 56.3, 74.9, 104.7, 122.9, 131.6, 133.8, 140.7, 159.1, 168.2.

IR (KBr): 1705 cm^{-1} .

HRMS: Calcd for $\text{C}_{19}\text{H}_{18}\text{INO}_4$ (M^+) 451.0279, found 451.0281.

(1S)-2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethylammonium chloride **4.19**



40 % aq MeNH_2 solution (33 mL) was added to a solution of the imide **4.17** (0.786 g, 1.74 mmol) in abs EtOH (50 mL). The reaction was heated at reflux for 1 h, then most of the EtOH was removed under reduced pressure. H_2O was added and the product extracted with Et_2O (x 4) and the combined organic extracts were concentrated to a volume of ca. 25 mL. The resulting solution was cooled to 0 °C and purged with HCl (g) for 15 min. The resulting white ppt was collected by filtration and dried under reduced pressure to give the title compound as a white solid (0.566 g, 91 %).

$[\alpha]_D^{20} + 12.6$ (c 2.50, MeOH)

Mp: 230-231 °C dec.

^1H NMR (500 MHz, CD_3OD): δ 1.30 [d, $J = 6.4$ Hz, 3H], 2.86 [dd, $J = 14, 7.8$ Hz, 1H], 2.95 [dd, $J = 14, 6.8$ Hz, 1H], 3.59 [m, 1H], 3.87 [s, 6H], 6.52 [s, 2H].

^{13}C NMR (75 MHz, CD_3OD): δ 18.9, 42.2, 50.4, 57.4, 76.8, 106.6, 140.2, 161.5.

IR (KBr): 1415, 3431 cm^{-1} .

HRMS: Electrospray Calcd for $\text{C}_{11}\text{H}_{17}\text{INO}_2$ (M^+) 322.0304, found 322.0319.

(1S)-N-[2-(4-Iodo-3,5-dimethoxyphenyl)-1-methylethyl]-acetamide 4.20



Dry NEt_3 (0.722 mL, 5.18 mmol) was added to a suspension of the hydrochloride **4.19** (0.842 g, 2.35 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. Freshly distilled AcCl (194 μL , 2.71 mmol) was slowly added and the reaction was warmed to r.t. overnight. The resulting solution was diluted with CH_2Cl_2 and washed with 1 M HCl solution (x 3). Removal of the solvent under reduced pressure gave the title compound as a white solid (0.817 g, 96 %).

$[\alpha]_D^{20} - 9.95$ (c 3.77, CHCl_3)

Mp: 142-143 °C.

^1H NMR (500 MHz, CDCl_3): δ 1.12 [d, $J = 6.4$ Hz, 3H], 1.94 [s, 3H], 2.65 [dd, $J = 14, 7.8$ Hz, 1H], 2.87 [dd, $J = 14, 5.4$ Hz, 1H], 3.86 [s, 6H], 4.26 [m, 1H], 5.33 [d, $J = 7.3$ Hz, 1H], 6.33 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 19.8, 23.2, 42.5, 45.8, 56.3, 74.8, 105.1, 140.5, 159.0, 169.2.

IR (KBr): 1570, 1630, 3076, 3242 cm^{-1} .

HRMS: Calcd for $\text{C}_{13}\text{H}_{19}\text{INO}_3$ (M^+) 364.0410, found 364.0411.

(3*S*)-7-Iodo-6,8-dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline 4.14

2,4,6-Collidine (173 μ L, 1.30 mmol) was added to a solution of the amide **4.20** (0.429 g, 1.18 mmol) in dry CH_3CN (6 mL). Freshly distilled POCl_3 (121 μ L, 1.30 mmol) was added and the reaction was heated at reflux for 3 h. The resulting solution was poured into sat aq NaHCO_3 solution and extracted with EtOAc (x 4). The solvent was removed under reduced pressure and purification by flash chromatography on alumina, eluting with 30 % EtOAc/petroleum ether, gave the title compound as a light tan solid (0.364 g, 89 %).

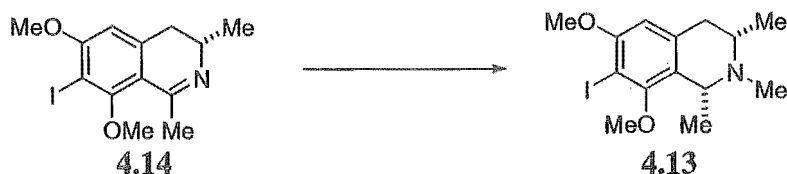
$[\alpha]_{\text{D}}^{20} + 33.7$ (c 3.68, CHCl_3)

Mp: 91-92 $^\circ\text{C}$.

^1H NMR (500 MHz, CDCl_3): δ 1.37 [d, $J = 6.8$ Hz, 3H], 2.30 [dd, $J = 16, 13$ Hz, 1H], 2.45 [d, $J = 2.0$ Hz, 3H], 2.61 [dd, $J = 16, 4.4$ Hz, 1H], 3.73 [s, 3H], 3.90 [s, 3H], 6.47 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 21.6, 25.7, 34.6, 51.3, 56.5, 61.9, 82.4, 105.9, 117.3, 142.5, 159.0, 160.2, 161.7.

HRMS: Calcd for $\text{C}_{13}\text{H}_{16}\text{INO}_2$ (M^+) 345.0225, found 345.0226.

(1*R*,3*S*)-7-Iodo-6,8-dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline 4.13

Iodomethane (212 μ L, 3.40 mmol) was added to a solution of the dihydroisoquinoline **4.14** (0.235 g, 0.680 mmol) in dry acetone (7 mL), followed by stirring at r.t. for 48 h. The solvent was removed under reduced pressure and the residue dissolved in dry CH_2Cl_2 and cooled to -78

°C. Neat DIBAL (145 μ L, 0.816 mmol) was added and the reaction allowed to warm to r.t. overnight. The reaction was quenched by dropwise addition of H₂O till coagulation occurred. The suspension was diluted with 1 M HCl solution, stirred for 5 min then neutralised with 1 M NaOH solution. The product was extracted with CH₂Cl₂ (x 4) and the solvent removed under reduced pressure. Purification by flash chromatography on alumina, eluting with 15 % EtOAc/petroleum ether, gave the title compound as a pale yellow solid (0.209 g, 85 %).

$[\alpha]_D^{20} + 52.2$ (c 4.18, CHCl₃)

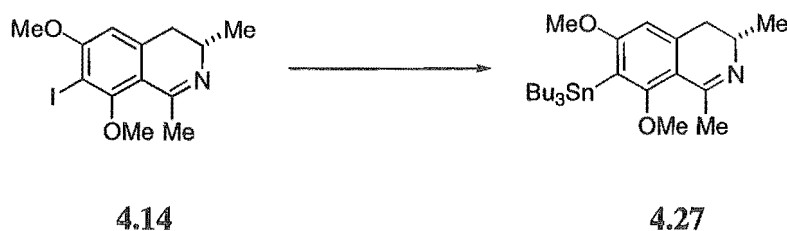
Mp: 79-80 °C.

¹H NMR (500 MHz, CDCl₃): δ 1.23 [d, J = 6.4 Hz, 3H], 1.40 [d, J = 6.8 Hz, 3H], 2.44 [m, 1H], 2.45 [s, 3H], 2.59 [dd, J = 16, 2.9 Hz, 1H], 2.67 [dd, J = 10, 16 Hz, 1H], 3.68 [q, J = 6.4 Hz, 1H], 3.79 [s, 3H], 3.85 [s, 3H], 6.38 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 21.3, 23.2, 38.3, 41.4, 55.0, 56.4, 57.5, 60.5, 81.2, 106.6, 126.7, 138.5, 157.0, 157.6.

HRMS: Calcd for C₁₄H₁₉INO₂ (M⁺) 360.0459, found 360.0461.

(3S)-6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-3,4-dihydroisoquinoline 4.27



A solution of *t*-BuLi in pentane (1.5 M, 0.707 mL, 1.06 mmol) was added dropwise to a solution of the iodide 4.14 (0.154 g, 0.424 mmol) in dry THF (4 mL) at – 95 °C. The reaction was stirred at – 95 °C for 15 min then ClSnBu₃ (0.288 mL, 1.06 mmol) was slowly added and the reaction allowed to warm to r.t. overnight. The resulting solution was poured into sat aq NaHCO₃ solution and extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification by flash chromatography on alumina, eluting with 15 % EtOAc/petroleum ether, gave the title compound as a colourless oil (0.179 g, 83 %).

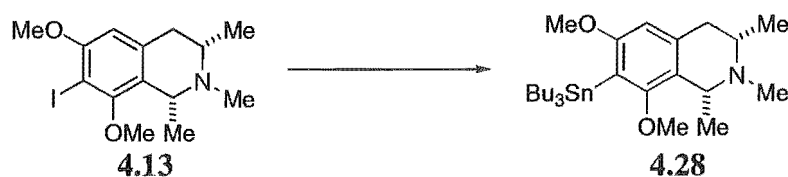
$[\alpha]_D^{20} + 26.1$ (c 3.75, CHCl_3)

^1H NMR (500 MHz, CDCl_3): δ 0.88 [m, 9H], 1.07 [m, 6H], 1.32 [m, 6H], 1.39 [d, $J = 6.8$ Hz, 3H], 1.51 [m, 6H], 2.33 [dd, $J = 16, 14$ Hz, 1H], 2.43 [d, $J = 2.0$ Hz, 3H], 2.60 [dd, $J = 16, 4.4$ Hz, 1H], 3.32 [m, 1H], 3.56 [s, 3H], 3.77 [s, 3H], 6.44 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 11.2, 13.6, 22.0, 25.5, 27.3, 29.1, 35.2, 51.6, 55.2, 63.1, 104.5, 117.0, 121.0, 144.0, 163.2, 164.9, 165.9.

HRMS: Calcd for $\text{C}_{25}\text{H}_{43}\text{NSnO}_2$ ($\text{M}^+ - \text{Bu}$) 452.1612, found 452.1612.

(1*R*,3*S*)-6,8-Dimethoxy-1,2,3-trimethyl-7-tributylstannanyl-1,2,3,4-tetrahydroisoquinoline 4.28



A solution of *t*-BuLi in pentane (1.5 M, 0.489 mL, 0.734 mmol) was added dropwise to a solution of the iodide **4.13** (0.106 g, 0.293 mmol) in dry THF (3 mL) at -95°C . The reaction was stirred at -95°C for 15 min then ClSnBu_3 (0.200 mL, 0.734 mmol) was slowly added and the reaction allowed to warm to r.t. overnight. The resulting solution was poured into sat aq NaHCO_3 solution and extracted with EtOAc ($\times 4$). The solvent was removed under reduced pressure and purification by flash chromatography on alumina, eluting with 5 % EtOAc/petroleum ether, gave the title compound as a colourless oil (87 mg, 56 %).

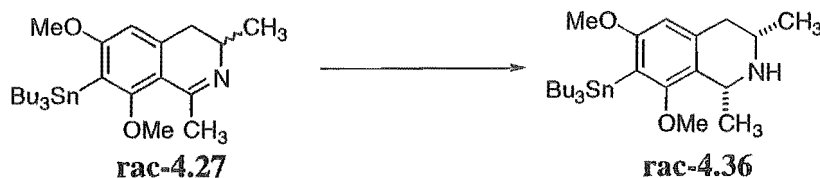
$[\alpha]_D^{20} + 40.0$ (c 1.62, CHCl_3)

^1H NMR (500 MHz, CDCl_3): δ 0.88 [m, 9H], 1.07 [m, 6H], 1.23 [d, $J = 6.4$ Hz, 1H], 1.32 [m, 6H], 1.41 [d, $J = 6.4$ Hz, 3H], 1.51 [m, 6H], 2.44 [m, 1H], 2.45 [s, 3H], 2.58 [dd, $J = 16, 2.6$ Hz, 1H], 2.71 [dd, $J = 16, 11$ Hz, 1H], 3.62 [s, 3H], 3.63 [m, 1H], 3.72 [s, 3H], 6.34 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 11.2, 13.7, 21.4, 23.3, 27.4, 29.2, 39.0, 41.4, 55.0, 55.2, 57.6, 61.8, 104.9, 119.7, 125.4, 139.3, 162.8, 163.5.

HRMS: Calcd for $\text{C}_{26}\text{H}_{47}\text{NSnO}_2$ ($\text{M}^+ - \text{CH}_3$) 510.2394, found 510.2394.

***rel*-(1*R*,3*S*)-6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-1,2,3,4-tetrahydroisoquinoline rac-4.36**



NaBH₄ (78 mg) was added to a solution of the dihydroisoquinoline **4.27** (0.179 g, 0.353 mmol) in MeOH (35 mL). The reaction was stirred for 30 min at r.t., following which the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ and filtered through a plug of celite. Removal of the solvent under reduced pressure gave the title compound as a colourless oil (0.173 g, 96 %).

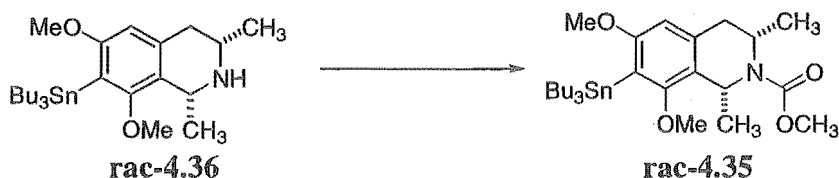
¹H NMR (500 MHz, CDCl₃): δ 0.87 [m, 9H], 1.04 [m, 6H], 1.21 [d, *J* = 6.4 Hz, 3H], 1.30 [m, 6H], 1.48 [d, *J* = 5.9 Hz, 3H], 1.50 [m, 6H], 2.48 [dd, *J* = 16, 11 Hz, 1H], 2.69 [dd, *J* = 16, 2.4 Hz, 1H], 2.91 [m, 1H], 3.57 [s, 3H], 3.70 [s, 3H], 4.25 [q, *J* = 6.4 Hz, 1H], 6.32 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 11.2, 13.7, 22.4, 22.6, 27.3, 29.2, 39.8, 48.3, 50.1, 55.0, 60.7, 105.8, 120.2, 125.3, 139.6, 162.8, 164.2.

IR (KBr): cm⁻¹.

HRMS: Calcd for C₁₇H₄₅NO₂Sn (M⁺ - Bu) 454.1768, found 454.1768.

rel*-(1*R*, 3*S*)-6,8-Dimethoxy-1,3-dimethyl-7-tributylstannanyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester **4.35*



NEt₃ (190 μL, 1.36 mmol) was added to a solution of the amine **rac-4.36** (0.178 g, 0.339 mmol) in dry CH₂Cl₂ at 0 °C. Methyl chloroformate (53 μL, 0.678 mmol) was added slowly and the reaction allowed to warm to r.t. overnight. The resulting solution was diluted with CH₂Cl₂ and washed with water. The solvent was removed under reduced pressure and the residue

purified by flash chromatography, eluting with 15 % EtOAc/petroleum ether, to give the title compound as a colourless oil (0.148 g, 77 %).

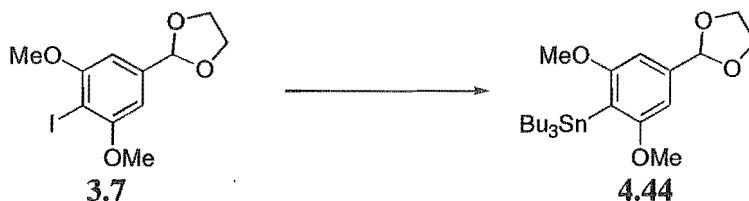
^1H NMR (500 MHz, CDCl_3): δ 0.87 [m, 9H], 1.08 [m, 6H], 1.31 [m, 6H], 1.38 [d, $J = 6.4$ Hz, 3H], 1.44 [d, $J = 7.3$ Hz, 3H], 1.50 [m, 6H], 2.88 [dd, $J = 16, 8.8$ Hz, 1H], 2.96 [dd, $J = 16, 6.8$ Hz, 1H], 3.67 [s, 3H], 3.71 [s, 3H], 3.72 [s, 3H], 4.16 [br m, 1H], 5.54 [br m, 1H], 6.41 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 11.1, 13.5, 22.0 (br), 24.0(br), 27.3, 29.2, 35.6, 46.5, 47.3, 52.3, 55.1, 62.6, 105.4, 120.0, 125.0 (br), 137.0, 156.1 (br), 162.2, 163.5.

IR (KBr): 1699 cm^{-1} .

HRMS: Calcd for $\text{C}_{27}\text{H}_{47}\text{NO}_4\text{Sn}$ ($\text{M}^+ - \text{Bu}$) 512.1823, found 512.1823.

Tributyl-[4-(1,3)-dioxolan-2-yl-2,6-dimethoxyphenyl]-stannane 4.44



A solution of *t*-BuLi in pentane (1.5 M, 10.2 mL, 15.2 mmol) was added dropwise *via* syringe to a stirred solution of the iodide **3.7** (2.05 g, 6.10 mmol) in dry THF (60 mL) at $-95\text{ }^\circ\text{C}$. The resulting solution was stirred at $-95\text{ }^\circ\text{C}$ for 15 min then ClSnBu_3 (4.13 mL, 15.2 mmol) was slowly added and the reaction allowed to warm slowly to r.t. overnight. The resulting solution was poured into sat aq NaHCO_3 solution, and extracted with EtOAc (x 4). Evaporation of the solvent under reduced pressure gave the crude product which was purified by flash chromatography on alumina, eluting with 5 % ethyl acetate/petroleum ether, to give the title compound as colourless oil (2.58 g, 85 %).

^1H NMR (500 MHz, CDCl_3): δ 0.87 [m, 9H], 1.01 [m, 6H], 1.30 [m, 6H], 1.48 [m, 6H], 3.75 [s, 3H], 4.00-4.17 [m, 4H], 5.80 [s, 1H], 6.62 [s, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 11.2, 13.7, 27.3, 29.1, 55.1, 65.2, 100.9, 103.7, 117.8, 140.8, 165.1.

HRMS: Calcd for $\text{C}_{23}\text{H}_{40}\text{O}_4^{120}\text{Sn}$ ($\text{M}^+ - \text{Bu}$) 443.1245, found 443.1244.

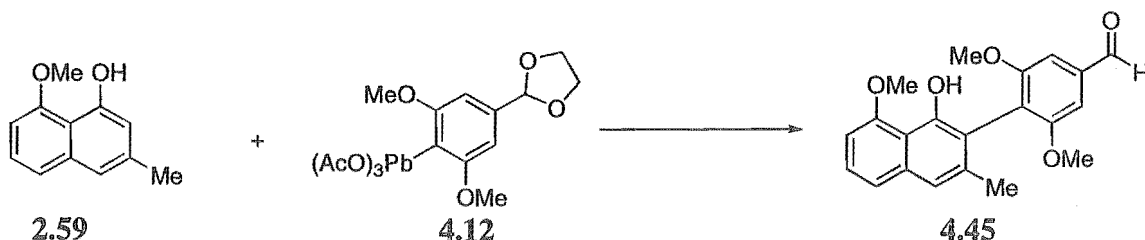
4-(1,3-Dioxolan-2-yl)-2,6-dimethoxyphenyl lead triacetate 4.12



Pb(OAc)₄ (95 %, 3.02g) was protected from light and stirred under high vacuum for 30 min. A solution of the stannane 4.44 (2.69 g, 5.39 mmol) and Hg(OAc)₂ (86 mg, 0.270 mmol) in dry CH₂Cl₂ (55 mL) was added *via* cannula and the reaction stirred at r.t. for 24 h. After this time the solution was diluted with CH₂Cl₂ and rinsed through a plug of celite. The solvent was removed under reduced pressure to give a residue, which was washed with petroleum ether (x 4). The resulting solid was dried under high vacuum to give the title compound as a light yellow solid (2.98 g, 93 %), which was used immediately in the next reaction.

¹H NMR (500 MHz, CDCl₃): δ 2.08 [s, 9H], 3.90 [s, 6H], 4.03-4.10 [m, 4H], 5.81 [s, 1H], 6.82 [s, 2H].

3,5-Dimethoxy-4-(1-hydroxy-8-methoxy-3-methylnaphthalen-2-yl)-benzaldehyde 4.45



Dry pyridine (1.34 mL) was added dropwise to a solution of the aryl-lead compound 4.12 (2.98 g, 5.02 mmol) and the naphthol 2.59 (0.945 g, 5.02 mmol) in dry CH₂Cl₂ (50 mL). The reaction was stirred at r.t., protected from light, for 24 h. After this time satd aq NH₄Cl solution was added and the aqueous layer was extracted with EtOAc (x 4). The combined organic extracts were washed with 1 M HCl solution. The solvent was removed under reduced pressure and the

residue dissolved in THF (100 mL). A solution of 3 % v/v aq H₂SO₄ solution (25 mL) was added and the reaction stirred vigorously for 1 h. The resulting solution was diluted with 1 M HCl solution and extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 40 % ethyl acetate/petroleum ether, gave the title compound as pale yellow solid (1.18 g, 67 %).

Mp: 196-197 °C.

¹H NMR (500 MHz, CDCl₃): δ 2.09 [s, 3H], 3.81 [s, 6H], 3.98 [s, 3H], 6.71 [d, *J* = 7.8 Hz, 1H], 7.22 [s, 2H], 7.24 [s, 1H], 7.27 [m, 1H], 7.35 [d, *J* = 8.3 Hz, 1H], 9.41 [s, 1H], 10.01 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 20.1, 55.8, 56.1, 103.1, 105.3, 113.2, 116.0, 118.5, 121.1, 122.0, 125.5, 136.1, 137.1, 137.2, 150.7, 156.0, 158.5, 191.9.

IR (KBr): 1697, 3500 cm⁻¹.

HRMS: Calcd for C₂₁H₂₀O₅ (M⁺) 352.1311, found 352.1311.

3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-benzaldehyde 4.46



A solution of the naphthol **4.45** (1.18 g, 3.34 mmol) in dry THF (45 mL) was added to a suspension of prewashed NaH (0.160 g, 6.68 mmol) in dry THF (10 mL). The reaction was stirred for 1 h at r.t. resulting in a turbid red solution. MOM-Cl (1.27 mL, 16.7 mmol) was added dropwise and the reaction was stirred at r.t. overnight. The reaction was poured into sat aq NaHCO₃ solution and extracted with EtOAc (x 4). The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 50 % EtOAc/petroleum ether, to give the title compound as a white solid (1.08 g, 81 %).

Mp: 177-178 °C.

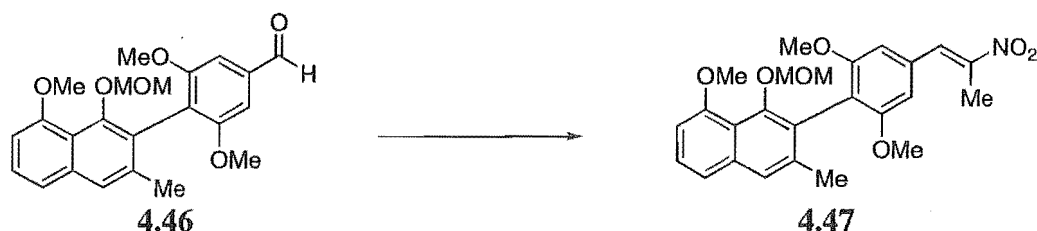
^1H NMR (500 MHz, CDCl_3): δ 2.09 [s, 3H], 2.80 [s, 3H], 3.79 [s, 6H], 3.95 [s, 3H], 4.86 [s, 2H], 6.80 [d, J = 6.8 Hz, 1H], 7.19 [s, 2H], 7.34 [dd, J = 8.3, 7.8 Hz, 1H], 7.38 [dd, J = 8.3, 1.5 Hz, 1H], 7.52 [s, 1H], 10.01 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 20.0, 55.9, 56.0, 56.1, 100.3, 104.8, 104.9, 118.6, 120.4, 122.9, 124.3, 126.0, 126.1, 136.1, 136.9, 137.1, 149.7, 155.8, 158.9.

IR (KBr): 1693 cm^{-1} .

HRMS: Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_6$ (M^+) 396.1573, found 396.1573.

(*E*)-2-[2,6-Dimethoxy-4-(2-nitropropenyl)-phenyl]-8-methoxy-1-methoxy-methoxy-3-methylnaphthalene 4.47



A solution of the aldehyde **4.46** (0.352 g, 0.888 mmol), ammonium acetate (37 mg), and glacial acetic acid (300 μL) in nitroethane (8 mL) was heated at reflux for 4h. The resulting solution was poured into sat aq NaHCO_3 solution and extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 30 % EtOAc/petroleum ether, gave the title compound as a yellow solid (0.371 g, 92 %).

Mp: 171-172 $^\circ\text{C}$.

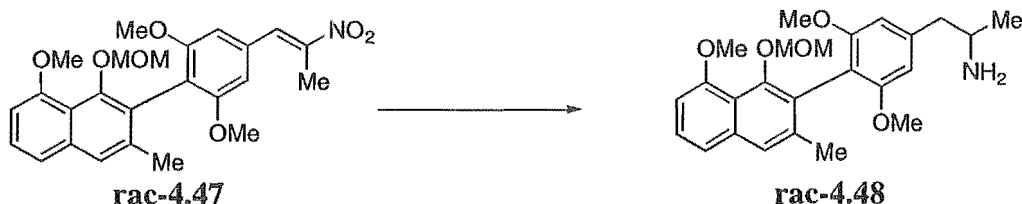
^1H NMR (500 MHz, CDCl_3): δ 2.12 [s, 3H], 2.54 [d, J = 0.98 Hz, 3H], 2.87 [s, 3H], 3.74 [s, 6H], 3.95 [s, 3H], 4.87 [s, 2H], 6.72 [s, 2H], 6.80 [m, 1H], 7.34 [m, 1H], 7.38 [m, 1H], 7.52 [s, 1H], 8.16 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 14.2, 20.1, 55.8, 55.9, 56.1, 100.2, 104.8, 105.4, 118.2, 118.6, 120.4, 124.2, 125.9, 126.1, 132.8, 134.1, 136.4, 136.8, 147.4, 149.8, 155.7, 158.4.

IR (KBr): $1516, 1568\text{ cm}^{-1}$.

HRMS: Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_7$ (M^+) 453.1788, found 453.1788.

(±)-2-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-1-methylethylamine rac-4.48



A solution of LiAlH_4 (1.0 M, 4.09 mL, 4.09 mmol) in THF was added to a solution of the nitrostyrene **4.47** (0.371 g, 0.817 mmol) in dry THF (20 mL). The reaction was heated at reflux for 3 h then quenched by slow addition of H_2O then 1 M NaOH solution. The product was extracted with EtOAc (x 4) and the combined organic extracts were washed with water. Removal of the solvent under reduced pressure gave the title compound as a white solid (0.333 g, 96 %).

Mp: 45-46 °C.

^1H NMR (500 MHz, CDCl_3): δ 1.18 [d, $J = 6.4$ Hz, 3H], 2.11 [s, 3H], 2.60 [dd, $J = 13, 8.3$ Hz, 1H], 2.78 [dd, $J = 13, 5.4$ Hz, 1H], 2.88 [s, 3H], 3.26 [m, 1H], 3.70 [s, 6H], 3.94 [s, 3H], 4.84 [s, 2H], 6.49 [s, 1H], 6.50 [s, 1H], 6.77 [d, $J = 7.3$ Hz, 1H], 7.30 [m, 1H], 7.36 [d, $J = 7.8$ Hz, 1H], 7.50 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 20.1, 23.0, 46.8, 48.4, 55.6, 55.7, 56.0, 99.7, 104.4, 104.5, 104.6, 113.5, 118.8, 120.3, 124.0, 125.5, 127.1, 136.5, 137.0, 140.4, 149.4, 155.7, 157.9, 158.0.

IR (KBr): 3416, 3551 cm^{-1} .

HRMS: Electrospray Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$ ($\text{M}^+ - \text{CH}_3\text{OH}$) 393.1940, found 393.1940.

(E)-3-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-acrylic acid ethyl ester 4.50



Triethyl phosphonoacetate (592 μL , 2.98 mmol) was added to a suspension of prewashed NaH (78 mg, 3.25 mmol) in dry benzene (8 mL) at 0 $^{\circ}\text{C}$. The reaction was stirred for 15 min then a solution of the aldehyde **4.46** (1.08 g, 2.71 mmol) in dry benzene (15 mL) was slowly added. The reaction was stirred for 1 h at 0 $^{\circ}\text{C}$, warmed to r.t. and stirred for a further 30 min, following which H_2O was added. The aqueous layer was extracted with EtOAc (x 4) and the combined organic extracts were washed with H_2O (x 2). Removal of the solvent under reduced pressure gave the title compound as a white solid (1.26 g, 100 %).

Mp: 181-182 $^{\circ}\text{C}$.

^1H NMR (500 MHz, CDCl_3): δ 1.37 [t, J = 7.1 Hz, 3H], 2.12[s, 3H], 2.84 [s, 3H], 3.74 [s, 6H], 3.94 [s, 3H], 4.30 [q, J = 7.1 Hz, 2H], 4.86 [s, 2H], 6.50 [d, J = 16 Hz, 1H], 6.78 [d, J = 7.3 Hz, 1H], 6.83 [s, 2H], 7.32 [dd, J = 8.3, 7.3 Hz, 1H], 7.35 [d, J = 7.3 Hz, 1H], 7.51 [s, 1H], 7.73 [d, J = 16 Hz, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 14.1, 20.0, 55.6, 55.7, 55.9, 60.3, 100.0, 103.3, 104.7, 117.8, 118.3, 118.6, 120.3, 124.0, 125.7, 126.4, 134.9, 136.5, 136.7, 144.8, 149.6, 155.6, 158.4, 166.7.

IR (KBr): 1709 cm^{-1} .

HRMS: Calcd for $\text{C}_{27}\text{H}_{30}\text{O}_7$ (M^+) 466.1992, found 466.1992.

(*E*)-3-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-prop-2-en-1-ol **4.51**



Neat DIBAL (1.00 mL, 5.61 mmol) was added dropwise to solution of the ester **4.50** (1.05 g, 2.24 mmol) in dry toluene (25 mL) at -78°C . The reaction was stirred for 15 min at this temperature. After this time EtOAc (100 mL) was added and the solution was allowed to warm to r.t. Sat aq NaHCO_3 solution was added and the solution stirred vigorously for 5 min, followed by filtration and separation of the layers. The aqueous layer was further extracted with EtOAc (x 3) and the organic extracts combined. Removal of the solvent under reduced pressure and

purification by flash chromatography, eluting with 60 % EtOAc/petroleum ether, gave the title compound as a white solid (0.844 g, 89 %).

Mp: 154-155 °C.

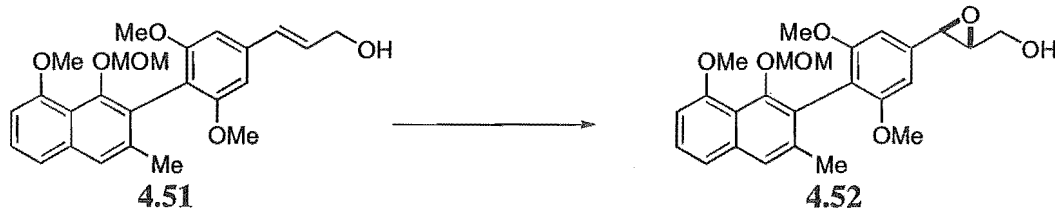
¹H NMR (500 MHz, CDCl₃): δ 2.11 [s, 3H], 2.87 [s, 3H], 3.72 [s, 6H], 3.94 [s, 3H], 4.36 [d, *J* = 4.9 Hz, 2H], 4.84 [s, 2H], 6.42 [m, 1H], 6.65 [d, *J* = 16 Hz, 1H], 6.69 [s, 2H], 6.77 [d, *J* = 6.8 Hz, 1H], 7.31 [m, 1H], 7.36 [d, *J* = 7.3 Hz, 1H], 7.50 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 20.1, 55.6, 55.7, 56.1, 63.1, 99.8, 101.9, 104.6, 115.2, 118.7, 120.3, 124.0, 125.6, 127.0, 128.5, 130.9, 136.6, 136.9, 137.5, 149.4, 155.6, 158.1.

IR (KBr): 3500 cm⁻¹.

HRMS: Calcd for C₂₅H₂₈O₆ (M⁺) 424.1886, found 424.1886.

(2*S*,3*R*)-{3-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-2,3-oxiranyl}-methanol 4.52



Ti(O^{*i*}Pr)₄ (20 uL, 0.068 mmol) was added to a solution of diisopropyl-*D*-tartrate (19 mg, 0.081 mmol) and powdered 4Å molecular sieves (40 mg) in dry CH₂Cl₂ (5 mL) at -20 °C. An anhydrous solution of TBHP in dry CH₂Cl₂ (6.1 M, 439 uL, 2.69 mmol) was added at a rate that maintained the internal temp at -20 °C. The reaction was stirred for 30 min at this temperature following which a solution of the allylic alcohol **4.51** (0.568 g, 1.34 mmol) in dry CH₂Cl₂ (6 mL), previously stirred over 4Å sieves for 30 min, was added at a rate as to maintain the internal temperature between -15 and -20 °C. The reaction was stirred for 5 h at -20 °C then 10 % aq NaOH solution, saturated with brine, was added, followed by Et₂O (15 mL). The solution was warmed to r.t. then dry MgSO₄ (2.6 g) and celite (0.33 g) were added. The suspension was stirred for 15 min, diluted with CH₂Cl₂, and filtered through a pad of celite, eluting with CH₂Cl₂. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting

with 60 % EtOAc/petroleum ether, gave the title compound as a white solid (0.474 g, 80 %, 90 % ee). Recrystallisation from toluene/petroleum ether gave (0.372 g, 63 %, > 95 % ee).

$[\alpha]_D^{20} + 13.8$ (c 3.99, CHCl₃)

Mp: 174-175 °C.

¹H NMR (500 MHz, CDCl₃): δ 1.83 [m, 3H], 2.09 [s, 3H], 2.86 [s, 3H], 3.25 [m, 1H], 3.71 [s, 6H], 3.85 [m, 1H], 3.94 [s, 3H], 3.99 [d, *J* = 2.0 Hz, 1H], 4.09 [m, 1H], 4.83 [s, 2H], 6.585 [s, 1H], 6.590 [s, 1H], 6.78 [d, *J* = 7.3 Hz, 1H], 7.31 [m, 1H], 7.36 [d, *J* = 7.3 Hz, 1H], 7.50 [s, 1H].

¹³C NMR (75 MHz, CDCl₃): δ 20.1, 55.7, 56.0, 56.1, 61.2, 62.5, 99.8, 100.8, 104.7, 115.5, 118.7, 120.3, 124.1, 125.6, 126.8, 136.6, 136.8, 137.9, 149.4, 155.6, 158.2.

IR (KBr): 3485 cm⁻¹.

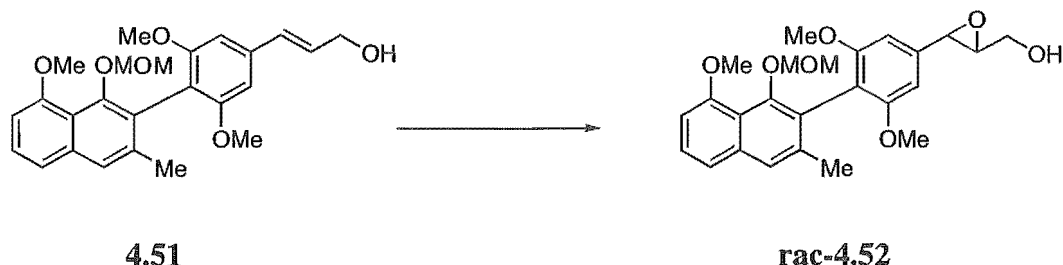
HRMS: electrospray Calcd for C₂₅H₂₈O₇ (M⁺ + Cl) 475.1524, found 475.1524.

Preparation and analysis of the Mosher esters derived from epoxide 4.52

Dry NEt₃ (5 μL), and a solution of (*S*)-MTPA-Cl (33 mg/mL) in dry CH₂Cl₂ (59 μL), were added to a solution of the epoxide 4.52 (3 mg) and DMAP (0.8 mg) in dry CH₂Cl₂ (0.5 mL). The reaction was stirred for 10 min at r.t., followed by TLC analysis to ensure complete consumption of starting material. The resulting solution was filtered through a short silica gel column, eluting with 40 % EtOAc/petroleum ether, and the solvent removed under reduced pressure. The enantiomeric excess for the epoxidation was determined by integration of the multiplets in the ¹H NMR spectrum (d1=5) at 3.31 and 3.33 ppm.

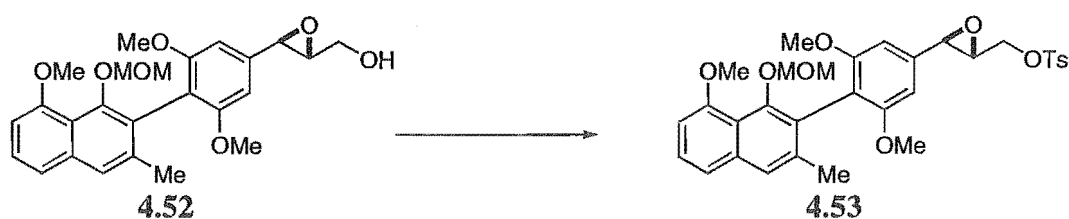
Major Diastereoisomer: ¹H NMR (500 MHz, CDCl₃): δ 2.08 [s, 3H], 2.84 [s, 3H], 3.33 [m, 1H], 3.60 [s, 3H], 3.69 [s, 3H], 3.70 [s, 3H], 3.86 [d, *J* = 1.5 Hz, 2H], 3.94 [s, 3H], 4.43 [dd, *J* = 12, 4.9 Hz, 1H], 4.77 [dd, *J* = 12, 3.4 Hz, 1H], 4.83 [s, 2H], 6.53 [s, 2H], 6.78 [d, *J* = 7.3 Hz, 1H], 7.31 [m, 1H], 7.36 [d, *J* = 7.8 Hz, 1H], 7.42 [m, 3H], 7.50 [s, 1H], 7.57 [m, 2H].

(±)-{3-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-2,3-oxiranyl}-methanol rac-4.52



Anhydrous TBHP solution (6.1 M, 6.72 mmol) in CH_2Cl_2 (18 μL) was added to a solution of the allylic alcohol **4.51** (23 mg, 0.16 mmol) and $\text{VO}(\text{acac})_2$ (0.3 mg, 0.31 μmol) in dry CH_2Cl_2 (0.5 mL). The reaction was stirred for 1 h at r.t., diluted with CH_2Cl_2 , and filtered through a plug of Celite. The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluting with 80 % EtOAc/petroleum ether, to give the title compound as a white solid (23 mg, 95 %), which was identical to the chiral material prepared above.

(2*S*,3*R*)-Toluene-4-sulfonic acid 3-[3,5-Dimethoxy-4-(8-methoxy-1-methoxy-methoxy-3-methyl-naphthalen-2-yl)-phenyl]-2,3-oxiranylmethyl ester 4.53



Dry NEt_3 (433 μL , 3.12 mmol) was added dropwise to a solution of the epoxy alcohol **4.52** (0.275 g, 0.623 mmol) and DMAP (76 mg, 0.623 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. A solution of TsCl (131 mg, 0.686 mmol) in dry CH_2Cl_2 (2 mL) was slowly added and the reaction stirred at 0 °C for 1 h. Sat aq NaHCO_3 solution was added and the product was extracted with EtOAc (x 4). The combined organic extracts were washed with satd aq NaHCO_3 solution. Removal of the solvent under reduced pressure gave the title compound as a fluffy white solid (0.307 g, 83 %).

$[\alpha]_D^{20} + 29.3$ (c 2.39, CHCl_3)

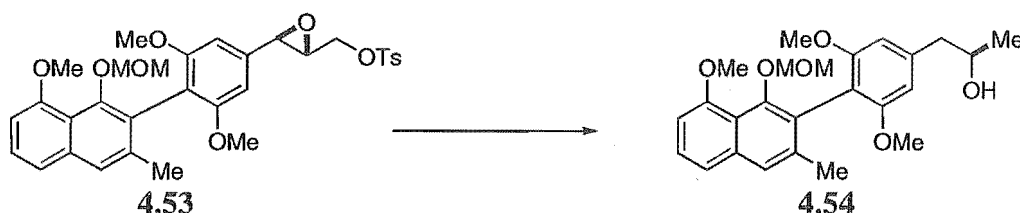
Mp: 80-81 °C.

^1H NMR (500 MHz, CDCl_3): δ 2.07 [s, 3H], 2.47 [s, 3H], 2.84 [s, 3H], 3.29 [m, 1H], 3.685 and 3.687 [s, 3H], 3.84 [d, $J = 2.0$ Hz, 2H], 3.94 [s, 3H], 4.16 [dd, $J = 11, 5.4$ Hz, 1H], 4.39 [dd, $J = 11, 3.4$ Hz, 1H], 4.82 [s, 2H], 6.51 [s, 1H], 6.53 [s, 1H], 6.77 [d, $J = 7.8$ Hz, 1H], 7.31 [t, $J = 7.8$ Hz, 1H], 7.36 [d, $J = 7.8$ Hz], 7.38 [d, $J = 8.3$ Hz, 2H], 7.49 [s, 1H], 7.85 [d, $J = 8.3$ Hz, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 20.1, 21.5, 55.7, 56.1, 56.6, 58.6, 69.2, 99.9, 100.6, 101.0, 104.7, 116.0, 118.7, 120.3, 124.1, 125.7, 126.7, 127.8, 129.9, 132.4, 136.6, 136.7, 136.8, 145.1, 149.6, 155.7, 158.3, 158.4.

HRMS: Calcd for $\text{C}_{32}\text{H}_{35}\text{O}_9$ ($\text{M}^+ + \text{H}$) 595.2002, found 595.1981.

(2*R*)-1-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-propan-2-ol 4.54



A solution of LiAlH_4 (1.0 M, 1.55 mL, 1.55 mmol) in THF was added dropwise to a solution of the tosylate 4.53 (0.307 g, 0.516 mmol) in dry Et_2O (50 mL) at 0 °C. The reaction was stirred for 2 h at 0 °C, then 30 min at r.t. The resulting solution was diluted with EtOAc and washed with sat aq NaHCO_3 solution. Removal of the solvent under reduced pressure and purification by flash chromatography, eluting with 80 % EtOAc /petroleum ether, gave the title compound as a fluffy white solid (0.206 g, 94 %).

$[\alpha]_D^{20} - 14.0$ (c 4.10, CHCl_3)

Mp: 94-95 °C.

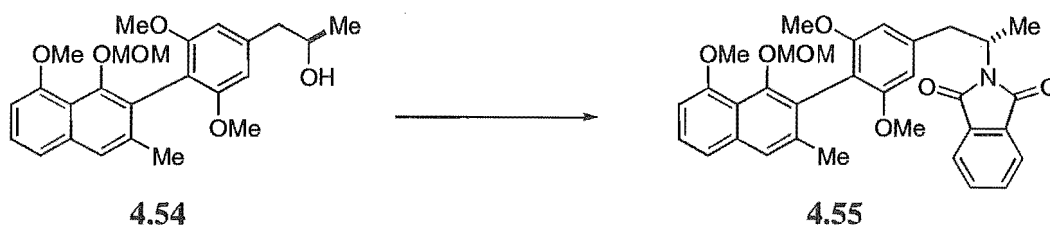
^1H NMR (500 MHz, CDCl_3): δ 1.29 [d, $J = 6.4$ Hz, 3H], 2.11 [s, 3H], 2.73 [dd, $J = 13, 8.3$ Hz, 1H], 2.85 [dd, $J = 13, 4.9$ Hz, 1H], 2.88 [s, 3H], 3.70 [s, 6H], 3.94 [s, 3H], 4.07 [m, 1H], 4.84 [s, 2H], 6.51 [s, 2H], 6.78 [d, $J = 7.3$ Hz, 1H], 7.31 [m, 1H], 7.36 [d, $J = 7.8$ Hz, 1H], 7.51 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 20.2, 22.6, 46.5, 55.8, 55.9, 56.1, 68.9, 99.9, 104.6, 104.7, 104.8, 113.9, 118.9, 120.4, 124.1, 125.6, 127.1, 136.7, 137.1, 139.5, 149.5, 155.8, 158.2, 158.3.

IR (film): 3427 cm^{-1} .

HRMS: Calcd for $\text{C}_{25}\text{H}_{30}\text{O}_6$ (M^+) 426.2042, found 426.2042.

(1S)-2-{2-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methyl-naphthalen-2-yl)-phenyl]-1-methylethyl}-isoindole-1,3-dione 4.55



DEAD (90 μL , 0.570 mmol) was added to a solution of the alcohol **4.54** (0.194 g, 0.456 mmol), PPh_3 (0.149 g, 0.570 mmol), and phthalimide (84 mg, 0.570 mmol) in dry THF (6 mL) at $0\text{ }^\circ\text{C}$. The reaction was protected from light and allowed to warm to r.t. overnight. Sat aq NaHCO_3 solution was added and the product extracted with EtOAc (x 4). The combined organic extracts were washed with sat aq NaHCO_3 solution. The solvent was removed under reduced pressure and the residue passed through a short column of alumina, eluting with 25 % EtOAc/petroleum ether. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, eluting with 40 % EtOAc/petroleum ether, gave the title compound as a white solid (0.207 g, 82 %).

$[\alpha]_{\text{D}}^{20} + 120$ (c 3.05, CHCl_3)

Mp: $82\text{--}85\text{ }^\circ\text{C}$.

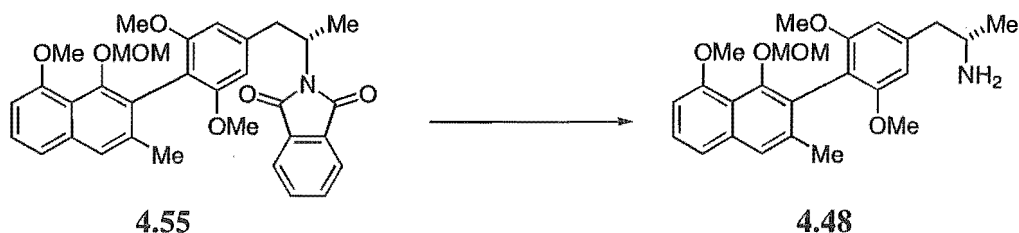
^1H NMR (500 MHz, CDCl_3): δ 1.60 [d, $J = 5.9\text{ Hz}$, 3H], 1.88 [s, 3H], 2.61 [s, 3H], 3.12 [dd, $J = 14, 5.9\text{ Hz}$, 1H], 3.43 [dd, $J = 11, 14\text{ Hz}$, 1H], 3.54 [s, 3H], 3.60 [s, 3H], 3.90 [s, 3H], 4.70–4.80 [overlapping m, 2H and 1H], 6.44 [s, 1H], 6.47 [s, 1H], 6.74 [d, $J = 7.3\text{ Hz}$, 1H], 7.27 [dd, $J = 7.8, 7.3\text{ Hz}$, 1H], 7.32 [d, $J = 7.8\text{ Hz}$, 1H], 7.43 [s, 1H], 7.67 [m, 2H], 7.75 [m, 2H].

^{13}C NMR (75 MHz, CDCl_3): δ 18.5, 19.8, 40.1, 48.2, 55.5, 55.6, 55.7, 55.8, 99.6, 104.0, 104.4, 104.5, 113.6, 118.6, 120.2, 122.7, 123.9, 125.4, 126.9, 131.6, 133.7, 136.5, 136.9, 139.2, 149.4, 155.6, 157.7, 157.8, 168.1.

IR (KBr): 1709, 1770 cm^{-1} .

HRMS: Calcd for $\text{C}_{33}\text{H}_{33}\text{O}_7$ (M^+) 555.2257, found 555.2257.

(1S)-2-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-1-methylethylamine 4.48



A solution of 40 % aq MeNH_2 (8 mL) was added to a solution of the imide **4.55** (0.234 g, 0.420 mmol) in abs EtOH (10 mL). The reaction was heated at reflux for 1 h, following which most of the EtOH was removed under reduced pressure. Sat aq NaHCO_3 solution was added and the product extracted with EtOAc (x 4). Removal of the solvent under reduced pressure gave the amine as a white solid (0.179 g, 100 %).

$[\alpha]_{\text{D}}^{20} + 13.8$ (c 3.58, CHCl_3)

Mp: 45-46 $^{\circ}\text{C}$.

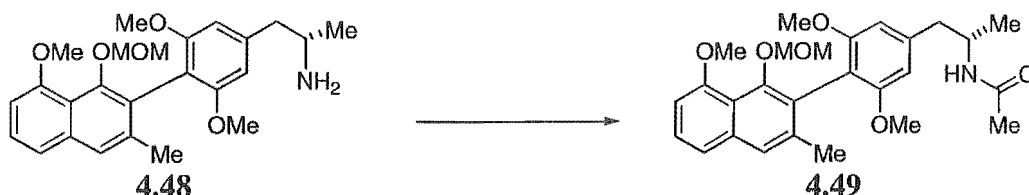
^1H NMR (500 MHz, CDCl_3): δ 1.18 [d, $J = 6.4$ Hz, 3H], 2.11 [s, 3H], 2.60 [dd, $J = 13, 8.3$ Hz, 1H], 2.78 [dd, $J = 13, 5.4$ Hz, 1H], 2.88 [s, 3H], 3.26 [m, 1H], 3.70 [s, 6H], 3.94 [s, 3H], 4.84 [s, 2H], 6.49 [s, 1H], 6.50 [s, 1H], 6.77 [d, $J = 7.3$ Hz, 1H], 7.30 [m, 1H], 7.36 [d, $J = 7.8$ Hz, 1H], 7.50 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 20.1, 23.0, 46.8, 48.4, 55.6, 55.7, 56.0, 99.7, 104.4, 104.5, 104.6, 113.5, 118.8, 120.3, 124.0, 125.5, 127.1, 136.5, 137.0, 140.4, 149.4, 155.7, 157.9, 158.0.

IR (KBr): 3416, 3551 cm^{-1} .

HRMS: Electrospray Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_5$ ($\text{M}^+ - \text{CH}_3\text{OH}$) 393.1940, found 393.1940.

(1*S*)-*N*-(2-[3,5-Dimethoxy-4-(8-methoxy-1-methoxymethoxy-3-methylnaphthalen-2-yl)-phenyl]-1-methylethyl)-acetamide 4.49



Dry NEt_3 (129 μL , 0.924 mmol) was added to a solution of the amine **4.48** (0.179 g, 0.420 mmol) in dry CH_2Cl_2 at 0 $^\circ\text{C}$. Freshly distilled AcCl (36 μL , 0.504 mmol) was added dropwise and the reaction allowed to warm slowly to r.t. overnight. The resulting solution was diluted with CH_2Cl_2 and washed with sat aq NaHCO_3 solution. Removal of the solvent under reduced pressure gave the title compound as a white solid (0.191 g, 97 %).

$[\alpha]_{\text{D}}^{20} + 16.7$ (c 1.10, CHCl_3)

Mp: 200-202 $^\circ\text{C}$.

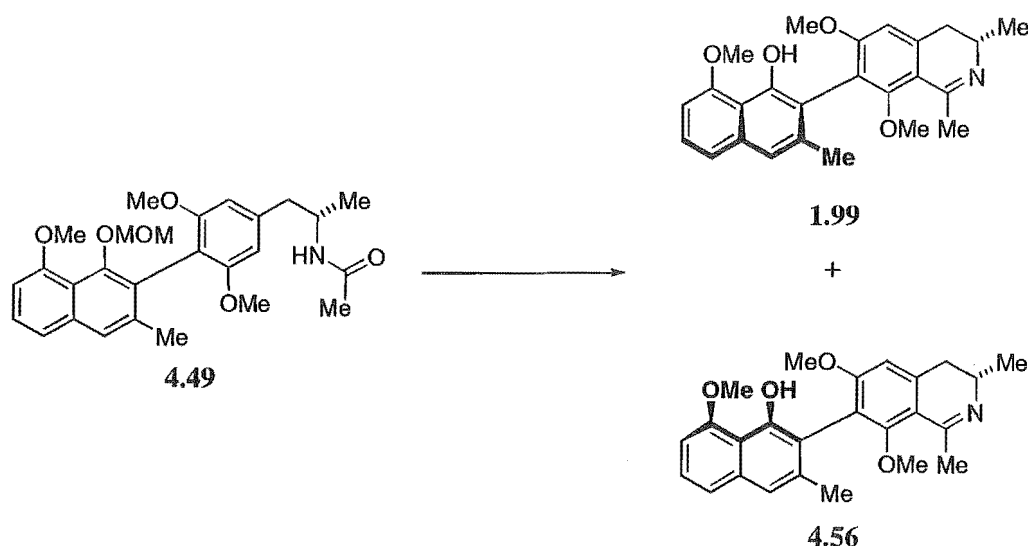
^1H NMR (500 MHz, CDCl_3): δ 1.15 [d, $J = 6.8$ Hz, 3H], 1.96 [s, 3H], 2.09 [s, 3H], 2.68 [dd, $J = 14, 7.8$ Hz, 1H], 2.87 [s, 3H], 2.94 [dd, $J = 13, 5.4$ Hz, 1H], 3.69 [s, 3H], 3.70 [s, 3H], 3.94 [s, 3H], 4.30 [m, 1H], 4.84 [m, 2H], 5.35 [d, $J = 7.8$ Hz, 1H], 6.46 [s, 1H], 6.49 [s, 1H], 6.77 [d, $J = 6.8$ Hz, 1H], 7.31 [m, 1H], 7.36 [d, $J = 7.3$ Hz, 1H], 7.50 [s, 1H].

^{13}C NMR (75 MHz, CDCl_3): δ 19.7, 20.1, 23.3, 43.2, 46.2, 55.7, 55.7, 56.1, 83.2, 99.8, 104.6, 104.6, 104.7, 113.7, 118.8, 120.3, 124.0, 125.5, 127.1, 136.6, 137.0, 139.2, 149.4, 155.7, 157.9, 158.0, 169.2.

IR (KBr): 1568, 1636, 3061, 3242, 3416 cm^{-1} .

HRMS: Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_6$ (M^+) 467.2308, found 467.2308.

***M*-(3*S*)-2-(6,8-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinolin-7-yl)-8-methoxy-3-methyl-naphthalen-1-ol 1.99 and *P*-atropisomer 4.56**



2,4,6-Collidine (58 μL , 0.437 mmol) was added to a solution of the amide **4.49** (0.186 g, 0.397 mmol) in dry CH_3CN (2 mL). Freshly distilled POCl_3 (41 μL , 0.437 mmol) was added and the reaction heated at reflux for 4 h. The resulting solution was cooled to r.t., poured into sat aq NaHCO_3 solution, and extracted with EtOAc (x 4). Removal of the solvent under reduced pressure and purification by flash chromatography on alumina, eluting with 50 % EtOAc/petroleum ether, gave the title compound as a 1:1 mixture of diastereoisomers (0.119 g, 74 %). The mixture was crystallised from toluene/petroleum ether. Concentration of the mother liquor and repeated crystallisation gave a further crop of crystals. Concentration of the mother liquor gave atropisomer **4.56** as a colourless gum shown to be 90 % diastereomerically pure by ^1H NMR spectroscopy. Further crystallisations did not improve the diastereomeric ratio.

$$[\alpha]_{\text{D}}^{20} + 40.4 \text{ (c 0.292, CHCl}_3\text{)}$$

^1H NMR (500 MHz, CDCl_3): δ 1.44 [d, $J = 6.8$ Hz, 3H], 2.19 [s, 3H], 2.43 [dd, $J = 15, 14$ Hz, 1H], 2.47 [d, $J = 2.0$ Hz, 3H], 2.67 [dd, $J = 16, 4.4$ Hz, 1H], 3.41 [s, 3H], 3.41 [m, 1H], 3.76 [s, 3H], 4.01 [s, 3H], 6.64 [s, 1H], 6.73 [d, $J = 7.3$ Hz, 1H], 7.27 [s, 1H], 7.29 [dd, $J = 8.3, 7.3$ Hz, 1H], 7.37 [d, $J = 8.3$ Hz, 1H], 9.59 [s, 1H].

^{13}C NMR (126 MHz, CDCl_3): δ 20.6, 22.4, 26.6, 35.3, 51.5, 55.9, 56.0, 61.2, 103.1, 105.9, 113.3, 117.0, 117.3, 118.8, 118.9, 121.3, 125.6, 136.2, 138.0, 141.5, 151.1, 156.1, 157.7, 159.3, 163.2.

IR (film): 3381 cm^{-1} .

HRMS: Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$ (M^+) 405.1940, found 405.1940.

The combined crops of crystals from above were recrystallised from toluene/petroleum ether to give Ancistrocladidine **1.99** as a single diastereoisomer as determined by ^1H NMR spectroscopy.

$[\alpha]_{\text{D}}^{20} - 136$ (c 1.84, CHCl_3) Lit $- 129.7$ (c 0.064, CHCl_3)⁴³ $- 149.3$ (c 1.13, CHCl_3)⁴⁰

Mp: 253-254 °C dec Lit (245-247 °C dec)⁴⁰ (255-258 dec)⁴³

^1H NMR (500 MHz, CDCl_3): δ 1.42 [d, $J = 6.8\text{ Hz}$, 3H], 2.16 [s, 3H], 2.45 [dd, $J = 15, 13\text{ Hz}$, 1H], 2.48 [d, $J = 2.0\text{ Hz}$, 3H], 2.68 [dd, $J = 15, 4.4\text{ Hz}$, 1H], 3.37 [s, 3H], 3.43 [m, 1H], 3.75 [s, 3H], 4.01 [s, 3H], 6.63 [s, 1H], 6.72 [d, $J = 7.3\text{ Hz}$, 1H], 7.25 [s, 1H], 7.28 [dd, $J = 8.3, 7.3\text{ Hz}$, 1H], 7.36 [d, $J = 8.3\text{ Hz}$, 1H], 9.61 [s, 1H].

^{13}C NMR (126 MHz, CDCl_3): δ 20.5, 22.0, 26.9, 35.2, 51.5, 55.8, 56.0, 60.9, 103.1, 105.9, 113.3, 116.9, 117.1, 118.7, 118.8, 121.1, 125.6, 136.2, 137.8, 141.3, 151.3, 156.1, 157.7, 159.2, 163.1.

IR (KBr): 3361 cm^{-1} .

HRMS: Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$ (M^+) 405.1940, found 405.1940.

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